

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

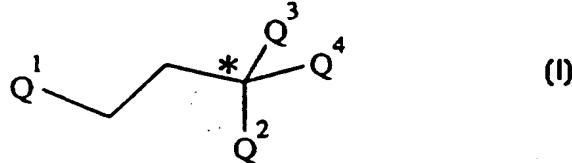
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ :		A1	(11) International Publication Number:	WO 97/19060
C07D 211/58, 211/52, 211/62; 211/76, 401/04, 211/66, A61K 31/445			(43) International Publication Date:	29 May 1997 (29.05.97)
(21) International Application Number:		PCT/GB96/02814	(81) Designated States:	AL, AM, AT; AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).
(22) International Filing Date:		15 November 1996 (15.11.96)		
(30) Priority Data:		9523526.3 17 November 1995 (17.11.95) GB	(Published)	With international search report.
(71) Applicant:		ZENECA LIMITED [GB/GB]; 15 Stanhope Gate, London W1Y 6LN (GB).		
(72) Inventors:		BERNSTEIN, Peter, Robert; Zeneca Inc., Legal & Intellectual Property Dept., 1800 Concord Pike, P.O. Box 15437, Wilmington, DE 19850-5437 (US). DEMBOFSKY, Bruce, Thomas; Zeneca Inc., Legal & Intellectual Property Dept., 1800 Concord Pike, P.O. Box 15437, Wilmington, DE 19850-5437 (US).		
(74) Agent:		BILL, Kevin; Zeneca Pharmaceuticals, Intellectual Property Dept., Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB).		

(54) Title: 3-(4-SUBST.-PIPERIDINYL-1)-1-(3,4-DICHLOROPHENYL)PROPYL CARBAMATES AND UREAS AND DERIVATIVES
AS NOVEL NEUROKININ ANTAGONISTS

(57) Abstract

Compounds of formula (I)
wherein Q¹, Q², Q³, and Q⁴ have
any of the meanings given in the
specification, their N-oxides, and their
pharmaceutically acceptable salts are
nonpeptide antagonists Substance P
and NKA, useful for the treatment
of asthma, etc. Also disclosed are
pharmaceutical compositions, processes
for preparing the compounds of formula
(I) and intermediates.





FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgyzstan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	KZ	Kazakhstan	SG	Singapore
CH	Switzerland	LI	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovakia
CM	Cameroon	LR	Liberia	SN	Senegal
CN	China	LT	Lithuania	SZ	Swaziland
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	LV	Latvia	TG	Togo
DE	Germany	MC	Monaco	TJ	Tajikistan
DK	Denmark	MD	Republic of Moldova	TT	Trinidad and Tobago
EE	Estonia	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	UG	Uganda
FI	Finland	MN	Mongolia	US	United States of America
FR	France	MR	Mauritania	UZ	Uzbekistan
GA	Gabon			VN	Viet Nam

3-(4-SUBST.-PIPERIDINYL-1)-1-(3,4-DICHLOROPHENYL)PROPYL CARBAMATES AND UREAS
AND DERIVATIVES AS NOVEL NEUROKININ ANTAGONISTS

This invention concerns novel piperidine derivatives which antagonize the pharmacological actions of the endogenous neuropeptide tachykinins known as neurokinins, particularly at the neurokinin 1 (NK1) and the neurokinin 2 (NK2) receptors. The novel piperidine derivatives are useful whenever such antagonism is desired. Thus, such compounds may be of value in the treatment of those diseases in which the NK1 and/or NK2 receptor is implicated, for example, in the treatment of asthma and related conditions. The invention also provides pharmaceutical compositions containing the novel piperidine derivatives for use in such treatment, methods for their use, and processes and intermediates for the manufacture of the novel piperidine derivatives.

The mammalian neurokinins comprise a class of peptide neurotransmitters which are found in the peripheral and central nervous systems. The three principal neurokinins are SP (SP), Neurokinin A (NKA) and Neurokinin B (NKB). There are also N-terminally extended forms of at least NKA. At least three receptor types are known for the three principal neurokinins. Based upon their relative selectivities favoring the neurokinin agonists SP, NKA and NKB, the receptors are classified as neurokinin 1 (NK1), neurokinin 2 (NK2) and neurokinin 3 (NK3) receptors, respectively. In the periphery, SP and NKA are localized in C-afferent sensory neurons, which neurons are characterized by non-myelinated nerve endings known as C-fibers, and are released by selective depolarization of these neurons, or selective stimulation of the C-fibers. C-Fibers are located in the airway epithelium, and the tachykinins are known to cause profound effects which clearly parallel many of the symptoms observed in asthmatics. The effects of release or introduction of tachykinins in mammalian airways include bronchoconstriction, increased microvascular permeability, vasodilation, increased mucus secretion and activation of mast cells. Thus, the tachykinins are implicated in the pathophysiology and airway hyperresponsiveness observed in asthmatics; and blockade of the action of released tachykinins may be useful in the treatment of asthma and related conditions. A cyclopeptide antagonist (FK-224) selective for both NK1 and NK2 receptors has demonstrated clinical efficacy in human patients suffering from asthma and chronic bronchitis. M. Ichinose, et al., Lancet, 1992, 340, 1248. Nonpeptidic tachykinin antagonists have been reported, for example in European Patent Application, Publication Number (EPA) 428434, EPA 474561.

EPA 512901, EPA 512902, EPA 515240 and EPA 559538, as well as in WO 94/10146, EPA 0625509, EPA 0630887, EPA 680962, WO 95/05377, WO 95/12577, WO 95/15961, and WO 95/16682. We have discovered a series of non-peptidic antagonists of the NK1 and NK2 receptors, and this is the basis for our invention.

According to the invention, there is provided a Compound of the invention which is a compound of formula I (formula set out hereinbelow following the Examples, together with other formulae denoted by Roman numerals) wherein

Q^1 is a radical selected from the group of radicals of formulae Ia, Ib, Ic, Id, Ie, If, Ig, Ih, Ij, Ik, and Im wherein

for a radical of formula Ia, Z^a is nitrogen or a group CR^{ad} in which R^{ad} is hydrogen or R^{ad} together with R^{ac} and the existing carbon to carbon bond forms a double bond; R^{aa} is Ar or Het; R^{ab} is hydrogen and R^{ac} is hydrogen or hydroxy or R^{ac} together with R^{ad} and the existing carbon to carbon bond forms a double bond, or R^{ac} and R^{ad} together form a diradical $-(CH_2)_j-$ in which j is an integer from 1 to 5; or R^{ab} and R^{ac} together form a diradical $-(CH_2)_k-$ in which k is an integer from 2 to 6, or R^{ab} and R^{ac} together are oxo or dialkylaminoalkyloxyimino of formula $=N-O-(CH_2)_q-NR^{ae}R^{af}$ in which q is the integer 2 or 3 and R^{ae} and R^{af} are independently hydrogen or (1-4C)alkyl, or the radical $NR^{ae}R^{af}$ is pyrrolidino, piperidino or morpholino;

for a radical of formula Ib, Z^b is a substituted imino group $R^{ba}N$ or $R^{ba}CH_2N$ in which R^{ba} is (3-7C)cycloakyl, Ar or Het; or Z^b is a disubstituted methylene group $R^{bb}(CH_2)_p-C-R^{bc}$ in which R^{bb} is Ar or Het; p is the integer 0 or 1; and R^{bc} is hydrogen, hydroxy, (1-4C)alkoxy, (1-4C)alkanoyloxy, $COOR^{bd}$ (wherein R^{bd} is hydrogen or (1-3C)alkyl), cyano, $NR^{be}R^{bf}$ or SR^{bg} in which R^{be} and R^{bf} are independently hydrogen, (1-4C)alkyl, (1-4C)hydroxyalkyl or (1-4C)alkanoyl, or the radical $NR^{be}R^{bf}$ is pyrrolidino, piperidino or morpholino; and R^{bg} is hydrogen or (1-4C)alkyl; or R^{bc} forms a double bond with the carbon atom to which it is bonded and with the adjacent carbon atom in the piperidine ring;

for a radical of formula Ic, R^{ca} is Ar or Het; and Z^c is oxo, thio, sulfinyl, sulfonyl or imino of formula $-NR^{cb}-$ in which R^{cb} is (1-3C)alkyl or $R^{cc}R^{cd}N-(CH_2)_q-$ in which q is the

integer 2 or 3 and in which R^{cc} and R^{cd} are independently hydrogen or (1-3C)alkyl or the radical $R^{cc}R^{cd}N$ is pyrrolidino, piperidino or morpholino;

for a radical of formula Id, R^{da} is 1, 2 or 3;

for a radical of formula Ie, J^e is oxygen, sulfur or NR^{ea} in which R^{ea} is hydrogen or (1-3C)alkyl; R^{eb} is hydrogen, (1-6C)alkyl which may bear a hydroxy substituent and/or one to three fluoro substituents, (3-6C)alkenyl (in which a vinyl carbon is not bound to nitrogen), 2-hydroxyethyl, (3-7C)cycloalkyl, Ar or Het; R^{ec} is hydrogen, (1-6C)alkyl which may bear a hydroxy substituent and/or one to three fluoro substituents, (3-6C)cycloalkyl, (1-5C)alkoxy (only when J^e is oxygen), (3-6C)cycloalkoxy (only when J^e is oxygen), or an amino group of formula $NR^{ed}R^{ee}$ containing zero to seven carbon atoms in which each of R^{ed} and R^{ee} is independently hydrogen, (1-5C)alkyl or (3-6C)cycloalkyl, or the radical $NR^{ed}R^{ee}$ is pyrrolidino, piperidino, morpholino, thiomorpholino (or its S-oxide) or piperazinyl (which piperazinyl group may bear a (1-3C)alkyl substituent at the 4-position);

for a radical of formula If, J^f is oxygen, sulfur or NR^{fa} in which R^{fa} is hydrogen or (1-3C)alkyl; L^f is a divalent hydrocarbon group in which the 1-position is bound to the carbon bearing the group J^f , the divalent group L^f being selected from trimethylene, cis-propenylene, tetramethylene, cis-butylene, cis-but-3-enylene, cis,cis-butadienylene, pentamethylene and cis-pentenylene which divalent group L^f itself may bear one or two methyl substituents;

for a radical of formula Ig, Z^g is (1-8C)alkyl or (3-8C)cycloalkyl which may bear one or more substituents selected from the group consisting of halo, (3-6C)cycloalkyl, cyano, nitro, hydroxy, (1-4C)alkoxy, (1-5C)alkanoyloxy, aroyl, heteroaroyl, oxo, imino (which may bear a (1-6C)alkyl, (3-6C)cycloalkyl, (1-5C)alkanoyl or aroyl substituent), hydroxyimino (which hydroxyimino may bear a (1-4C)alkyl or a phenyl substituent on the oxygen), an amino group of formula $NR^{ga}R^{gb}$, an amino group of formula $NR^{gc}R^{gd}$, an amidino group of formula $C(=NR^{gg})NR^{ge}R^{gf}$, and a carbamoyl group of formula $CON(OR^{gh})R^{gi}$, but excluding any radical wherein a hydroxy and an oxo substituent together form a carboxy group, wherein an amino group of formula $NR^{ga}R^{gb}$ contains zero to seven carbon atoms and each of R^{ga} and R^{gb} is independently hydrogen, (1-5C)alkyl or (3-6C)cycloalkyl, or the radical $NR^{ga}R^{gb}$ is pyrrolidino, piperidino, morpholino, thiomorpholino (or its S-oxide) or piperazinyl (which

- 4 -

piperazinyl may bear a (1-3C)alkyl substituent group at the 4-position); and wherein R^g^c is hydrogen or (1-3C)alkyl and R^g^d is (1-5C)alkanoyl, aroyl or heteroaroyl; or R^g^d is a group of formula C(=J^g)NR^g^eR^g^f in which J^g is oxygen, sulfur, NR^g^g or CHR^g^h; and wherein the amino group NR^g^eR^g^f contains zero to seven carbon atoms and each of R^g^c and R^g^f is independently hydrogen, (1-5C)alkyl or (3-6C)cycloalkyl, or the radical NR^g^eR^g^f is pyrrolidino, piperidino, morpholino, thiomorpholino (or its S-oxide) or piperazinyl (which piperazinyl may bear a (1-3C)alkyl substituent at the 4-position) or R^g^e is hydrogen or (1-4C)alkyl and R^g^f together with R^g^g forms an ethylene or trimethylene group; R^g^g is hydrogen, (1-4C)alkyl or together with R^g^f forms an ethylene or trimethylene group; R^g^h is cyano, nitro or SO₂R^g^k and R^g^k is (1-4C)alkyl or phenyl; R^g^l and R^gⁱ are independently (1-3C)alkyl; and in which a cyclic group which is a substituent on Z^g or formed by substitution on Z^g may bear one or more (1-3C)alkyl groups on carbon as further substituents; and in which any aryl or heteroaryl group which is a part of the group Z^g may bear one or more halo, (1-4C)alkyl, (1-4C)alkoxy, cyano, trifluoromethyl or nitro substituents;

for a radical of formula I^h, G^h denotes a single bond, a double bond or a divalent hydrocarbon radical; J^h denotes a radical joined to the ring by a single bond if G^h denotes a double bond or, otherwise, a radical joined by a double bond; M^h denotes a heteroatom, a substituted heteroatom, or a single bond; and L^h denotes a hydrocarbon radical in which the 1-position is attached to M^h; wherein the values of G^h, J^h, M^h and L^h are selected from

(a) G^h is a single bond; J^h is oxo or thioxo; M^h is oxy, thio or NR^{ha}; and L^h is L^{ha};

(b) G^h is a single bond; J^h is NR^{hb}; M^h is NR^{ha}; and L^h is L^{ha};

(c) G^h is a double bond, J^h is OR^{ha}, SR^{ha} or NR^{hc}R^{hd}; M^h is nitrogen; and L^h is L^{ha};

(d) G^h is methylene which may bear one or two methyl substituents; J^h is oxo, thioxo or NR^{he}; M^h is oxy, thio, sulfinyl, sulfonyl or NR^{ha}; and L^h is L^{hb};

(e) G^h is a single bond; J^h is oxo, thioxo or NR^{he}; M^h is nitrogen; and L^h is L^{hc};

(f) G^h is methine, which may bear a (1-3C)alkyl substituent; J^h is oxo, thioxo or NR^{he} ; M^h is nitrogen; and L^h is L^{hd} ; (g) G^h is cis-vinylene, which may bear one or two methyl substituents; J^h is oxo, thioxo, or NR^{he} ; M^h is nitrogen; and L^h is L^{he} ; and

(h) G^h is a single bond; J^h is oxo or thioxo; M^h is a single bond; and L^h is L^{hf} ;

5 wherein

R^{ha} is hydrogen or (1-3C)alkyl; R^{hb} is hydrogen, (1-3C)alkyl, cyano, (1-3C)alkylsulfonyl or nitro; R^{hc} and R^{hd} are independently hydrogen or (1-3C)alkyl or the radical $NR^{hc}R^{hd}$ is pyrrolidino, piperidino, morpholino, thiomorpholino (or its S-oxide) or piperazinyl (which piperazinyl may bear a (1-3C)alkyl substituent at the 4-position); R^{he} is hydrogen or (1-3C)alkyl; L^{ha} is ethylene, cis-vinylene, trimethylene or tetramethylene which radical L^{ha} itself may bear one or two methyl substituents; L^{hb} is ethylene or trimethylene which radical L^{hb} itself may bear one or two methyl substituents; L^{hc} is prop-2-en-1-yliden-3-yl, which radical L^{hc} itself may bear one or two methyl substituents; L^{hd} is cis-vinylene, which radical L^{hd} itself may bear one or two methyl substituents; L^{he} is methine, which radical L^{he} itself may bear a (1-3C)alkyl substituent; and L^{hf} is 4-oxabutan-1,4-diyil;

10 for a radical of formula Ij. X^j is (1-6C)alkyl, $-CH_2OR^{ja}$, $-CH_2SR^{ja}$, $-CH_2S(O)R^{je}$, $-CH_2S(O)_2R^{je}$, $-COR^{ja}$, $-COOR^{ja}$, $-C(=J^{ja})NR^{jb}R^{jc}$, $-C(R^{ja})(OR^{jd})(OR^{je})$,
 $-CH_2N(R^{ja})C(=J^{ja})R^{jf}$, $-CH_2N(R^{ja})COOR^{je}$ or $-CH_2N(R^{ja})C(=J^{ja})NR^{jb}R^{jc}$;
 B^j is a direct bond and L^j is a hydrocarbon chain in which the 1-position is bound to B^j and L^j is selected from trimethylene, tetramethylene, cis-1-buteneylene and cis,cis-butadienylene; or B^j is $N(R^{jh})$ and L^j is a hydrocarbon chain selected from ethylene, trimethylene and cis-vinylene; or B^j is N and L^j is a hydrocarbon chain in which the 1-position is bound to B^j and L^j is cis,cis-prop-2-en-1-ylidin-3-yl; J^j and J^{ja} are independently oxygen or sulfur; R^{ja} , R^{jf} and R^{jh} are independently hydrogen or (1-6C)alkyl; R^{jb} and R^{jc} are independently hydrogen or (1-6C)alkyl; or the radical $NR^{jb}R^{jc}$ is pyrrolidino, piperidino, morpholino, thiomorpholino (or its S-oxide) or piperazinyl (which piperazinyl may bear a (1-3C)alkyl substituent at the 4-position); R^{jd} and R^{je} are independently (1-3C)alkyl or together form a divalent hydrocarbon chain selected from ethylene and trimethylene; R^{je} is (1-6C)alkyl;

- 6 -

for a radical of formula I^k , Z^k is a nitrogen linked radical of formula II wherein E^1 , E^2 , E^3 and E^4 form a divalent four membered chain ($-E^1=E^2-E^3=E^4-$) in which each of E^1 , E^2 , E^3 and E^4 is methine; or in which one or two of E^1 , E^2 , E^3 and E^4 is nitrogen and the remaining E^1 , E^2 , E^3 and E^4 are methine; and further wherein one or more of E^1 , E^2 , E^3 and E^4 which is methine may bear a halo, (1-3C)alkyl, hydroxy, (1-3C)alkoxy, (1-3C)alkylthio, (1-3C)alkylsulfinyl or (1-3C)alkylsulfonyl substituent; and wherein the radicals F^k , G^k , and $I^k(X^k)$ are selected from

(a) G^k is a direct bond, $I^k(X^k)$ is a radical having the formula $=C(Z^k)-$ and F^k is a radical selected from $-CH=$ and $-N=$;

10 (b) G^k is a direct bond, $I^k(X^k)$ is a radical having the formula $-C(=J^k)-$ and F^k is a radical selected from $-N(R^{kf})-$, $-CH_2-CH_2-$, $-CH=CH-$, $-CH_2-N(R^{kf})-$ and $-CH=N-$;

(c) G^k is a radical having the formula $-CH_2-$, $I^k(X^k)$ is a radical having formula $-C(=J^k)-$ and F^k is selected from $-CH_2-$ and $-N(R^{kf})-$; and

(d) G^k is selected from $-CH_2-$, $-CH_2-CH_2-$, $-CH=CH-$ and $-N=CH-$, $I^k(X^k)$ is a radical having the formula $-C(=J^k)-$ and F^k is a direct bond; wherein

J^k is oxygen or sulfur; Z^k is $-OR^{ka}$, $-SR^{ka}$, $-COR^{ka}$, $-COOR^{ka}$, $-C(=J^{ka})NR^{kb}R^{kc}$ or $-C(R^{ka})(OR^{kd})(OR^{ke})$; J^{ka} is oxygen or sulfur; R^{ka} and R^{kf} are independently hydrogen or (1-6C)alkyl; R^{kb} and R^{kc} are independently hydrogen or (1-6C)alkyl; or the radical $NR^{kb}R^{kc}$ is pyrrolidino, piperidino, morpholino, thiomorpholino (or its S-oxide) or piperazinyl (which

20 piperazinyl may bear a (1-3C)alkyl substituent at the 4-position); R^{kd} and R^{ke} are independently (1-3C)alkyl or R^{kd} and R^{ke} together form ethylene or trimethylene; or Z^k is an imido radical selected from phthalimido, succinimido, maleimido, glutarimido, and 3-oxa-, 3-thia- and 3-azaglutarimido, in which the imido radical may bear one or more (1-3C)alkyl substituents and, in addition, the aromatic portion of the phthalimido may bear one or more halo, hydroxy or (1-3C)alkoxy substituents; and

for a radical of formula Im , R^{ma} and R^{mb} are independently selected from the group consisting of hydrogen, (1-3C)alkyl, (3-6C)cycloalkyl, phenyl, benzyl, and phenethyl; and R^{mc} is pyrrolidino, piperidino, morpholino, thiomorpholino (or its S-oxide), piperazinyl (which

piperazinyl may bear a (1-3C)alkyl substituent at the 4-position); or R^{mc} is -NR^{md}R^{me}, wherein R^{md} and R^{me} are independently selected from hydrogen, (1-3C)alkyl, phenyl, benzyl and phenethyl; and wherein

for a radical Q¹, Ar is a phenyl radical or an ortho-fused bicyclic carbocyclic radical of nine of ten ring atoms in which at least one ring is aromatic, which radical Ar may be unsubstituted or may bear one or more substituents selected from halo, cyano, trifluoromethyl, (1-4C)alkyl, (1-4C)alkoxy, methylenedioxy, hydroxy, mercapto, -S(O)_nR^{xa}, (1-5C)alkanoyl, (1-5C)alkanoyloxy, nitro, NR^{xb}R^{xc}, NR^{xd}R^{xe}, C(=NR^{xf})NR^{xg}R^{xh}, CONR^{xb}R^{xc} and COOR^{xj} wherein n is the integer 0, 1, or 2; R^{xa} is (1-6C)alkyl, (3-6C)cycloalkyl or phenyl (which phenyl may bear a halo, trifluoromethyl, (1-3C)alkyl or (1-3C)alkoxy substituent); the radical NR^{xb}R^{xc} contains zero to seven carbons and each of R^{xb} and R^{xc} is independently hydrogen, (1-5C)alkyl or (3-6C)cycloalkyl, or the radical NR^{xb}R^{xc} is pyrrolidino, piperidino, morpholino, thiomorpholine (or its S-oxide) or piperazinyl (which piperazinyl may bear a (1-3C)alkyl substituent at the 4-position); and wherein R^{xd} is hydrogen or (1-4C)alkyl and R^{xe} is (1-5C)alkanoyl, benzoyl; or a group of formula C(=J^x)NR^{xg}R^{xh} in which J^x is oxygen, sulfur, NR^{xf} or CHR^{xi}; R^{xf} is hydrogen, (1-5C)alkyl or together with R^{xg} forms an ethylene or trimethylene diradical, the radical NR^{xg}R^{xh} contains zero to 7 carbons and each of R^{xg} and R^{xh} is independently hydrogen, (1-5C)alkyl or (3-6C)cycloalkyl, or the radical NR^{xg}R^{xh} is pyrrolidino, piperidino, morpholino, thiomorpholine (or its S-oxide) or piperazinyl (which piperazinyl may bear a (1-3C)alkyl substituent at the 4-position); or R^{xg} together with R^{xf} forms an ethylene or trimethylene diradical and R^{xh} is hydrogen or (1-5C)alkyl; R^{xi} is cyano, nitro, (1-5C)alkylsulfonyl or phenylsulfonyl; and R^{xj} is hydrogen, (1-5C)alkyl or benzyl; and Het is a radical (or stable N-oxide thereof) attached via a ring carbon of a monocyclic aromatic ring containing five or six ring atoms consisting of carbon and one to four heteroatoms selected from oxygen, sulfur and nitrogen, or an ortho-fused bicyclic heterocycle derived therefrom by fusing a propenylene, trimethylene, tetramethylene or benz-diradical, which radical Het may be unsubstituted or may be substituted on carbon by one or more of the substituents defined above for Ar and may be substituted on nitrogen by (1-3C)alkyl;

- 8 -

Q² is a group B or CH₂B wherein B is phenyl which may bear one or two substituents independently selected from halo, trifluoromethyl, hydroxy, (1-3C)alkoxy, (1-3C)alkyl and methylenedioxy; or B is thienyl, imidazolyl, benzo[b]thiophenyl or naphthyl any of which may bear a halo substituent; or B is biphenylyl; or B is carbon-linked indolyl which 5 may bear a benzyl substituent at the 1-position;

Q³ is hydrogen, or (1-4C)alkyl; and

Q⁴ is a radical selected from -OC(=O)NR³R⁴, -N(R⁶)C(=O)OR², -N(R⁶)C(=O)NR³R⁴, -N(R⁶)C(=O)SR⁵, -SC(=O)NR³R⁴, -N(R⁶)C(=O)R¹⁵, and -OC(=O)R¹⁶ wherein

10 R² and R⁵ are independently (1-6C)alkyl, (3-7C)cycloalkyl, aryl, heteroaryl, aryl(1-3C)alkyl, heteroaryl(1-3C)alkyl or a radical of formula XV, wherein any aryl or heteroaryl group or radical of formula XV may bear one, two or three substituents independently selected from halo, trifluoromethyl, hydroxy, (1-3C)alkoxy, (1-3C)alkyl, cyano, -NR⁷R⁸, C(=O)NR⁹R¹⁰, -S(=O)NR¹¹R¹², -S(=O)₂NR¹¹R¹², and methylenedioxy, and further wherein any arylethyl, 15 arylpropyl, heteroarylethyl or heteroarylpropyl group may optionally be substituted at the position a to the aryl or heteroaryl group by a group selected from oxo, and =NOR¹³;

R³ and R⁴ are independently selected from hydrogen, (1-6C)alkyl,

(3-7C)cycloalkyl, aryl, heteroaryl, aryl(1-3C)alkyl, heteroaryl(1-3C)alkyl, and a radical of formula XV, wherein any aryl or heteroaryl group, or radical of formula XV may bear one two or 20 three substituents independently selected from halo, trifluoromethyl, hydroxy, (1-3C)alkoxy, (1-3C)alkyl, cyano, -NR⁷R⁸, C(=O)NR⁹R¹⁰, -S(=O)NR¹¹R¹², -S(=O)₂NR¹¹R¹², and methylenedioxy, and further wherein any arylethyl, arylpropyl, heteroarylethyl or heteroarylpropyl group may optionally be substituted at the position a to the aryl or heteroaryl group by a group selected from oxo, and =NOR¹³; or

25 -NR³R⁴ taken together represents a cyclic amino radical selected from pyrrolidinyl, piperidino, 1,2,3,6-tetrahydro-pyridyl, 1,2,3,4-tetrahydroquinolyl, 1,2,3,4-tetrahydroisoquinolyl, which cyclic amino radical may bear one or two substituents independently selected from halo, trifluoromethyl, hydroxy, (1-3C)alkoxy, (1-3C)alkyl, cyano.

- 9 -

$-\text{NR}^7\text{R}^8$, $-\text{C}(=\text{O})\text{NR}^9\text{R}^{10}$, $-\text{S}(=\text{O})\text{NR}^{11}\text{R}^{12}$, $-\text{S}(=\text{O})_2\text{NR}^{11}\text{R}^{12}$, phenyl, acetamidomethyl, and methylenedioxy;

R^{15} and R^{16} are independently (1-6C)alkyl, (3-7C)cycloalkyl, aryl, heteroaryl, aryl(1-3C)alkyl, heteroaryl(1-3C)alkyl, or a radical of formula XV, wherein any aryl or heteroaryl group or radical of formula XV may bear one, two or three substituents independently selected from halo, trifluoromethyl, hydroxy, (1-3C)alkoxy, (1-3C)alkyl, cyano, $-\text{NR}^7\text{R}^8$, $\text{C}(=\text{O})\text{NR}^9\text{R}^{10}$, $-\text{S}(=\text{O})\text{NR}^{11}\text{R}^{12}$, $-\text{S}(=\text{O})_2\text{NR}^{11}\text{R}^{12}$, and methylenedioxy,

E is selected from $-\text{O}-$, $-\text{S}-$, $-\text{N}(\text{R}^{14})-$, $-\text{S}(=\text{O})-$ and $-\text{S}(\text{O})_2-$;

m is 1, 2, or 3; and

$\text{R}^6\text{--R}^{14}$ are independently selected from hydrogen and (1-3C)alkyl;

or the N-oxide of a piperidino nitrogen in Q¹;

or a pharmaceutically acceptable salt thereof;

or a quaternary ammonium salt thereof in which the piperidino nitrogen in Q¹ is a quadricovalent ammonium nitrogen wherein the fourth radical on the nitrogen R¹ is (1-4C)alkyl or benzyl and the associated counterion A is a pharmaceutically acceptable anion; provided that the compound of formula I is not N-phenyl-1-(2,4-dichlorophenyl)-3-piperidinopropyl carbamate, N-phenyl-1-(4-methylphenyl)-3-piperidinopropyl carbamate, N-(1-isopropyl-1-naphthyl-3-piperidinopropyl)ethyl carbamate, N-phenyl-1-phenyl-3-piperidinopropyl carbamate, N-phenyl-1-phenyl-3-pyrrolidinopropyl carbamate, N-ethyl-1-phenyl-3-piperidinopropyl carbamate, or N-phenyl-1-(4-propoxyphenyl)-3-piperidinopropyl carbamate.

A preferred sub-set of compounds of the invention are compounds of formula I wherein:

Q¹ is selected from radicals of formulae Ia, Ib, Ic, Id, Ie, If, Ig, Ih, Ij and Ik; and Q⁴ is a radical selected from $-\text{OC}(=\text{O})\text{NR}^3\text{R}^4$, $-\text{N}(\text{R}^6)\text{C}(=\text{O})\text{OR}^2$, $-\text{N}(\text{R}^6)\text{C}(=\text{O})\text{NR}^3\text{R}^4$,

$-\text{N}(\text{R}^6)\text{C}(=\text{O})\text{SR}^5$, and $-\text{SC}(=\text{O})\text{NR}^3\text{R}^4$;

R² and R⁵ are independently (1-6C)alkyl, (3-7C)cycloalkyl, aryl, heteroaryl, aryl(1-3C)alkyl, or heteroaryl(1-3C)alkyl, wherein any aryl or heteroaryl group may bear one, two or three substituents independently selected from halo, trifluoromethyl, hydroxy, (1-3C)alkoxy, (1-3C)alkyl, cyano, $-\text{NR}^7\text{R}^8$, $\text{C}(=\text{O})\text{NR}^9\text{R}^{10}$, $-\text{S}(=\text{O})\text{NR}^{11}\text{R}^{12}$, $-\text{S}(=\text{O})_2\text{NR}^{11}\text{R}^{12}$,

-10-

and methylenedioxy, and further wherein any arylethyl, arylpropyl, heteroarylethyl or heteroarylpropyl group may optionally be substituted at the position *a* to the aryl or heteroaryl group by a group selected from oxo, and =NOR¹³; and

m is 1 or 2;

5 or the N-oxide of a piperidino nitrogen in Q¹;
 or a pharmaceutically acceptable salt thereof;
 or a quaternary ammonium salt thereof in which the piperidino nitrogen in Q¹ is a quadricovalent ammonium nitrogen wherein the fourth radical on the nitrogen R¹ is (1-4C)alkyl or benzyl and the associated counterion A is a pharmaceutically acceptable anion.

10 Another preferred sub-set of compounds of the invention are compounds of formula I wherein:

Q¹ is 4-acetamido-4-phenylpiperidino, 4-(2-methylsulfinylphenyl)piperidino, 4-(2-oxopiperidino)piperidino, or 4-(2-oxoperhydropyrimidin-1-yl)piperidino;

15 Q² is a group B or -CH₂B wherein B is phenyl which may bear one or two substituents independently selected from halo, trifluoromethyl, hydroxy, (1-3C)alkoxy, (1-3C)alkyl and methylenedioxy; or B is thienyl, imidazolyl, benzo[b]thiophenyl or naphthyl any of which may bear a halo substituent; or B is biphenylyl; or B is carbon-linked indolyl which may bear a benzyl substituent at the 1-position;

Q³ is hydrogen; and

20 Q⁴ is a radical selected from -OC(=O)NR³R⁴, -N(R⁶)C(=O)OR², -N(R⁶)C(=O)NR³R⁴, -N(R⁶)C(=O)SR⁵, and -SC(=O)NR³R⁴; wherein

25 R² and R⁵ are independently (1-6C)alkyl, (3-7C)cycloalkyl, aryl, heteroaryl, aryl(1-3C)alkyl or heteroaryl(1-3C)alkyl, wherein any aryl or heteroaryl group may bear one, two or three substituents independently selected from halo, trifluoromethyl, hydroxy, (1-3C)alkoxy, (1-3C)alkyl, cyano, -NR⁷R⁸, C(=O)NR⁹R¹⁰, -S(=O)NR¹¹R¹², -S(=O)₂NR¹¹R¹², and methylenedioxy;

30 R³ and R⁴ are independently selected from hydrogen, (1-6C)alkyl, (3-7C)cycloalkyl, aryl, heteroaryl, aryl(1-3C)alkyl, heteroaryl(1-3C)alkyl, and a radical of formula XV, wherein any aryl or heteroaryl group, or radical of formula XV may bear one two or

- 11 -

three substituents independently selected from halo, trifluoromethyl, hydroxy, (1-3C)alkoxy, (1-3C)alkyl, cyano, -NR⁷R⁸, C(=O)NR⁹R¹⁰, -S(=O)NR¹¹R¹², -S(=O)₂NR¹¹R¹², and methylenedioxy; or

-NR³R⁴ taken together represents a cyclic amino radical selected from 5 pyrrolidinyl, piperidino, 1,2,3,6-tetrahydro-pyridyl, 1,2,3,4-tetrahydroquinolyl, 1,2,3,4-tetrahydroisoquinolyl, which cyclic amino radical may bear one or two substituents independently selected from halo, trifluoromethyl, hydroxy, (1-3C)alkoxy, (1-3C)alkyl, cyano, -NR⁷R⁸, -C(=O)NR⁹R¹⁰, -S(=O)NR¹¹R¹², -S(=O)₂NR¹¹R¹², phenyl, acetamidomethyl, and methylenedioxy;

10 E is -O-;

m is 1 or 2; and

R⁶-R¹² and R¹⁴ are independently selected from hydrogen and (1-3C)alkyl;

or the N-oxide of a piperidino nitrogen in Q¹;

15 or a pharmaceutically acceptable salt thereof;

or a quaternary ammonium salt thereof in which the piperidino nitrogen in Q¹ is a quadricovalent ammonium nitrogen wherein the fourth radical on the nitrogen R¹ is (1-4C)alkyl or benzyl and the associated counterion A is a pharmaceutically acceptable anion.

It will be appreciated that a compound of formula I may contain one or more 20 asymmetrically substituted carbon atoms and that such a compound may be isolated in optically active, racemic and/or diastereomeric forms. A compound may exhibit polymorphism. It is to be understood that the present invention encompasses any racemic, optically-active, diastereomeric, polymorphic or stereoisomeric form, or mixture thereof, which form possesses NK1 and NK2 antagonist properties, it being well known in the art how to prepare 25 optically-active forms (for example, by resolution of the racemic form or by synthesis from optically-active starting materials) and how to determine the NK1 and NK2 antagonist properties by the standard tests known in the art and those described hereinafter. It may be preferred to use the compound of formula I in a form which is characterized as containing, for example, at least 95%, 98% or 99% enantiomeric excess of the form which is of the (S)-configuration at the 30 center indicated by * in formula I.

- 12 -

In this specification R¹, R², et cetera stand for generic radicals and have no other significance. It is to be understood that the generic terms "(1-3C)alkyl" and "(1-6C)alkyl" include both straight and branched chain alkyl radicals but references to individual alkyl radicals such as "propyl" embrace only the straight chain ("normal") radical, branched chain isomers such as "isopropyl" being referred to specifically. A similar convention applies to other generic groups, for example, alkoxy, alkanoyl, et cetera. Halo is fluoro, chloro, bromo or iodo. Aryl denotes a phenyl radical or an ortho-fused bicyclic carbocyclic radical having about nine to ten ring atoms in which at least one ring is aromatic. Heteroaryl encompasses a radical attached via a ring carbon of a monocyclic aromatic ring containing five ring atoms, consisting of carbon and one to four heteroatoms selected from oxygen, sulfur and nitrogen or containing six ring atoms consisting of carbon and one or two nitrogens, as well as a radical of an ortho-fused bicyclic heterocycle of about eight to ten atoms derived therefrom, particularly a benz-derivative or one derived by fusing a propenylene, trimethylene or tetramethylene diradical thereto, as well as a stable N-oxide thereof.

Particular values listed below for radicals, substituents and ranges are for illustration only and they do not exclude other defined values or other values within defined ranges for the radicals and substituents.

A particular value for Ar is phenyl which may be unsubstituted or may bear a chloro, methyl, methoxy, hydroxy or methylsulfinyl substituent. A particular value for Het is furyl, thienyl, 2-imidazolyl, 1,3,4-oxadiazol-2-yl, pyridyl or pyrimidinyl which ring may be unsubstituted or may bear a chloro, methyl, methoxy, hydroxy, methylsulfinyl, methoxycarbonyl or ethoxycarbonyl substituent. A particular value for aryl is phenyl. A particular value for heteroaryl is furyl, pyridyl, imidazolyl, indolyl or pyrimidinyl. A particular value for halo is chloro or bromo. A particular value for (1-3C)alkyl is methyl, ethyl, propyl or isopropyl; for (1-4C)alkyl is methyl, ethyl, propyl, isopropyl, butyl, isobutyl or t-butyl; for (1-5C)alkyl is methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl or isopentyl; for (1-6C)alkyl is methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, hexyl or isohexyl; and for (1-8C)alkyl is methyl, ethyl, propyl, isopropyl, isopentyl, 1-ethylpropyl, hexyl, isohexyl, 1-propylbutyl, or octyl. A particular value for (3-6C)cycloalkyl is cyclopropyl, cyclopentyl or cyclohexyl; for (3-7C)cycloalkyl is cyclopropyl, cyclopentyl, cyclohexyl or cycloheptyl; and for (3-8C)cycloalkyl is cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl. A particular

-13-

value for (3-6C)alkenyl is allyl, 2-but enyl or 3-methyl-2-but enyl. A particular value for (1-4C) alkanoyl is formyl, acetyl, propionyl, butyryl or isobutyryl; and for (1-5C) alkanoyl is formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl or pivaloyl.

A more particular value for Ar is phenyl which may be unsubstituted or may bear
5 a methoxy, hydroxy or methylsulfinyl substituent. A more particular value for Het is pyridyl or pyrimidinyl which ring may be unsubstituted or may bear a methoxy, hydroxy or methylsulfinyl substituent. A more particular value for heteroaryl is pyridyl; halo is chloro. A more particular value for (1-3C) alkyl is methyl; for (1-4C) alkyl is methyl or ethyl; for (1-5C) alkyl is methyl, ethyl, propyl or isopropyl; for (1-6C) alkyl is methyl, ethyl, propyl, isopropyl, butyl, isobutyl or
10 t-butyl; and for (1-8C) alkyl is methyl, ethyl, propyl, isopropyl, 1-ethylpropyl or 1-propylbutyl. A more particular value for (3-6C)cycloalkyl is cyclopropyl or cyclopentyl; for (3-7C)cycloalkyl is cyclopropyl or cyclopentyl; and for (3-8C)cycloalkyl is cyclopropyl, cyclopentyl, cyclohexyl or cycloheptyl. A more particular value for (3-6C) alkenyl is allyl. A more particular value for (1-4C) alkanoyl is formyl or acetyl; and for (1-5C) alkanoyl is formyl, acetyl, propionyl, butyryl or
15 isobutyryl.

A particular value for Q¹ is 4-hydroxy-4-phenylpiperidino, 4-acetamido-4-phenylpiperidino, 4-(2-methylsulfinylphenyl)piperidino, 4-(2-oxopiperidino)-piperidino, or 4-(2-oxoperhydropyrimidin-1-yl)piperidino; for Q² is 3,4-dichlorophenyl, or 3,4-methylenedioxyphe nyl; for Q³ is hydrogen; and for Q⁴ is N-benzylcarbamoyloxy, N-[(S)- α -methylbenzyl]carbamoyloxy, 3-methyl-3-(2-methoxybenzyl)ureido, phenethylcarbonyloxy, 3-indan-1-ylureido, 2-methoxyphenethylcarbonylamino, and 2-methoxybenzyloxy-carbonylamino.

A more particular value for Q¹ is 4-acetamido-4-phenyl-piperidino.

A more particular value for Q⁴ is N-benzylcarbamoyloxy, N-[(S)- α -methylbenzyl]carbamoyloxy, and 3-methyl-3-(2-methoxybenzyl)ureido.,

A particular value for Q² is 3,4-dichlorophenyl, or 3,4-methylenedioxyphe nyl.

A particular value for E is -O-.

A particular group of compounds of formula I are compounds wherein Q¹ is selected from radicals of formulae Ia, Ib, Ic, Id, If, Ig, Ih, Ij, Ik, and Im.

A particular group of compounds of formula I are compounds wherein Q¹ is selected from radicals of formulae Ia, Ic, Id, If, Ig, Ih, Ij, Ik, and Im.

-14-

A particular group of compounds of formula I are compounds wherein Q¹ is selected from radicals of formulae Ia, Ib, Ic, Ie, If, Ig, Ih, Ij and Ik.

A particular group of compounds of formula I are compounds wherein Q¹ is selected from radicals of formulae Ie, If, Ig, Ih, Ij, Ik and Im.

5 A particular group of compounds of formula I are compounds wherein Q¹ is selected from radicals of formulae Ie, If, Ig, Ih, Ij and Ik.

A particular group of compounds of formula I are compounds wherein Q¹ is a radical of formula Ia.

10 A particular group of compounds of formula I are compounds wherein Q¹ is a radical of formula Ib.

A particular group of compounds of formula I are compounds wherein Q¹ is a radical of formula Ic.

A particular group of compounds of formula I are compounds wherein Q¹ is a radical of formula Id.

15 A particular group of compounds of formula I are compounds wherein Q¹ is a radical of formula Ie.

A particular group of compounds of formula I are compounds wherein Q¹ is a radical of formula If.

20 A particular group of compounds of formula I are compounds wherein Q¹ is a radical of formula Ig.

A particular group of compounds of formula I are compounds wherein Q¹ is a radical of formula Ih.

A particular group of compounds of formula I are compounds wherein Q¹ is a radical of formula Ij.

25 A particular group of compounds of formula I are compounds wherein Q¹ is a radical of formula Ik.

A particular group of compounds of formula I are compounds wherein Q¹ is a radical of formula Im.

-15-

A particular group of compounds are compounds of formula I wherein Q¹ is a radical of formula Ib wherein Z^b is a disubstituted methylene group R^{bb}(CH₂)_p-C-R^{bc}.

A particular group of compounds of formula I are compounds wherein Q⁴ is -OC(=O)NR³R⁴.

5 A particular group of compounds of formula I are compounds wherein Q⁴ is -N(R⁶)C(=O)OR².

A particular group of compounds of formula I are compounds wherein Q⁴ is -N(R⁶)C(=O)NR³R⁴.

10 A particular group of compounds of formula I are compounds wherein Q⁴ is -N(R⁶)C(=O)SR⁵.

A particular group of compounds of formula I are compounds wherein Q⁴ is -SC(=O)NR³R⁴.

A particular group of compounds of formula I are compounds wherein Q⁴ is -N(R⁶)C(=O)R¹⁵.

15 A particular group of compounds of formula I are compounds wherein Q⁴ is -OC(=O)R¹⁶.

A particular group of compounds of formula I are compounds wherein R², R³, R⁴ and R⁵ are independently selected from (1-6C)alkyl and (3-7C)cycloalkyl.

20 A particular group of compounds of formula I are compounds wherein R², R³, R⁴ and R⁵ are independently selected from aryl, heteroaryl, aryl(1-3C)alkyl or heteroaryl(1-3C)alkyl, wherein any aryl or heteroaryl group may bear one, two or three substituents independently selected from halo, trifluoromethyl, hydroxy, (1-3C)alkoxy, (1-3C)alkyl, cyano, -NR⁷R⁸, C(=O)NR⁹R¹⁰, -S(=O)NR¹¹R¹², -S(=O)₂NR¹¹R¹², and methylenedioxy.

25 A more particular group of compounds of formula I are compounds of formula III wherein Q¹ is selected from radicals of formulae Ie, If, Ig, Ih, Ij, Ik and Im.

A more particular group of compounds of formula I are compounds of formula III wherein Q¹ is selected from radicals of formulae Ie, If, Ig, Ih, Ij and Ik.

A more particular group of compounds of formula I are compounds of formula III wherein Q⁴ is, -OC(=O)NR³R⁴.

A more particular group of compounds of formula I are compounds of formula III wherein Q⁴ is -N(R⁶)C(=O)OR².

5 A more particular group of compounds of formula I are compounds of formula III wherein Q⁴ is -N(R⁶)C(=O)NR³R⁴.

A more particular group of compounds of formula I are compounds of formula III wherein Q⁴ is -N(R⁶)C(=O)SR⁵.

10 A more particular group of compounds of formula I are compounds of formula III wherein Q⁴ is -SC(=O)NR³R⁴.

A more particular group of compounds of formula I are compounds of formula III wherein Q⁴ is, -N(R⁶)C(=O)R¹⁵.

A more particular group of compounds of formula I are compounds of formula III wherein Q⁴ is -OC(=O)R¹⁶.

15 Pharmaceutically acceptable salts of a compound of formula I include those made with a strong inorganic or organic acid which affords a physiologically acceptable anion, such as, for example, hydrochloric, sulfuric, phosphoric, methanesulfonic, or para-toluenesulfonic acid.

A compound of formula I may be made by processes which include processes known in the chemical art for the production of structurally analogous heterocyclic compounds.

20 Such processes for the manufacture of a compound of formula I as defined above are provided as further features of the invention and are illustrated by the following procedures in which the meanings of generic radicals are as defined above unless otherwise indicated:

(a) For a compound of formula I wherein Q⁴ is an oxygen linked radical -OC(=O)NR³R⁴, reacting an alcohol of formula VII with a suitable isocyanate of formula 25 OCNR³R⁴, under standard conditions. The reaction may conveniently be carried out, for example, using conditions similar to those described in Example 1.

(b) Alkylating an amine of formula Q¹H with an aldehyde of formula XIV by reductive alkylation. The alkylation may conveniently be carried out by the in situ acid-catalyzed formation of an imminium salt, followed by reduction with a suitable reducing agent such as for example sodium cyanoborohydride in alcoholic solvent.

(c) For an acid addition salt of a compound of formula I, treating a corresponding compound of formula I which is in the free-base form, with an acid. The salt may conveniently be formed in a suitable solvent, such as for example diethyl ether, benzene or toluene.

5 (d) For an N-oxide of a piperidino nitrogen in Q¹, oxidizing the piperidino nitrogen of a corresponding compound of formula I using a conventional procedure, such as, for example, using hydrogen peroxide in methanol, peracetic acid, 3-chloroperoxybenzoic acid in an inert solvent (such as dichloromethane) or dioxirane in acetone.

10 (e) For a quaternary ammonium salt of the piperidino nitrogen in Q¹, alkylating the piperidino nitrogen in a corresponding compound of formula I with an alkylating agent of formula R¹Z wherein Z is a leaving group, such as for example, a chloro, bromo, iodo, tosyl, tosylates, mesyl or trifyl group.

(f) For a compound of formula I which bears a sulfinyl group, oxidizing the sulfur of a corresponding compound of formula I which bears a sulfide group using a conventional method.

15 (g) For a compound of formula I which bears a sulfonyl group, oxidizing a sulfide or sulfinyl group of a corresponding compound of formula I using a conventional method.

(h) For a compound of formula I which bears an aromatic hydroxy group, cleaving the ether of a corresponding compound of formula I which bears an aromatic alkoxy group using a conventional method.

20 (i) For a compound of formula I wherein Q⁴ is an oxygen linked radical -OC(=O)R¹⁶, reacting an alcohol of formula VII with a suitable acid chloride of formula ClC(=O) R¹⁶ or an equivalent activated acid derivative, under standard conditions. The reaction may conveniently be carried out, for example, using conditions similar to those described in Example 41.

25 (j) For a compound of formula I wherein Q⁴ is an oxygen linked radical -NC(=O)R¹⁵, reacting an amine of formula IX with a suitable acid chloride of formula ClC(=O) R¹⁵ or an equivalent activated acid derivative, under standard conditions.

-18-

It may be desired to optionally use a protecting group during all or portions of the above described processes; the protecting group then may be removed when the final compound is to be formed.

Whereafter, for any of the above procedures, when a pharmaceutically acceptable salt of a compound of formula I is required, it may be obtained by reacting the compound of formula I with an acid affording a physiologically acceptable counterion or by any other conventional procedure.

It will also be appreciated that certain of the various optional substituents in the compounds of the invention may be introduced by standard aromatic substitution reactions or generated by conventional functional group modifications either prior to or immediately following the processes above, and as such are included in the process aspect of the invention. The reagents and reaction conditions for such procedures are well known in the chemical art.

If not commercially available, the necessary starting materials for the above procedures may be made by procedures which are selected from standard techniques of organic chemistry, techniques which are analogous to the synthesis of known, structurally similar compounds and techniques which are analogous to the above described procedures or the procedures described in the Examples. As will be clear to one skilled in the art, a variety of sequences are available for the preparation of the starting materials, and the sequences leading to the starting materials and products of the invention may be altered if appropriate considerations regarding the synthetic methods and radicals present are followed. The starting materials, intermediates and the procedures for their preparation are additional aspects of the invention. Intermediates of formula VII, IX, or XIV, wherein the radicals Q1, Q2, Q3, Q4, etc. have any of the values, particular values, or more particular values listed herein above, are particularly useful for preparing compounds of the invention.

An alcohol of formula VII may be prepared from a hydrochloride salt of formula $Q^1H \cdot HCl$ as shown in Scheme I. Treatment with aqueous formaldehyde followed by acetic anhydride gives a transient hemi-aminal intermediate of formula IV, which can be treated directly with a ketone of formula V to give a ketone of formula VI. Reduction of the ketone VI, for example, using sodium borohydride, yields the desired alcohol.

An amine of formula IX may be prepared from a ketone of formula VI as shown in Scheme II. Conversion of the ketone to an imide of formula VIII followed by reduction of the

-19-

imide using standard conditions such as for example, reduction with diimide, gives the desired amine of formula IX. As shown in Scheme II, an amine of formula IX may also be prepared directly from an alcohol of formula VII using standard conditions, such as for example, by treatment with triphenylphosphine and diethyl azodicarboxylate. An amine of formula IX may 5 also be prepared from an alcohol of formula VII via a phthalimido compound of formula X as shown in Scheme II. Conversion of the alcohol functionality to a suitable leaving group, followed by displacement with a phthalimido nucleophile, gives a compound of formula X, which may be converted to an amine of formula IX using standard conditions.

An aldehyde of formula XIV wherein Q⁴ is a nitrogen linked radical, can be 10 prepared as outlined in Scheme III. An acid of formula XI may be converted to an iso-cyanate of formula XII under standard conditions, such as for example by treatment with diphenylphosphoryl azide and triethylamine in toluene at 100 °C. The iso-cyanate can be converted to an alkene of formula XIII by treatment with a nucleophile (Y) of formula -OR², -SR⁵ or -NH(R³)(R⁴), using standard conditions. Oxidative cleavage of the alkene gives an 15 aldehyde of formula XIV, wherein Q⁴ is a nitrogen linked radical. The oxidative cleavage may conveniently be carried out under standard conditions, such as for example by treatment with sodium periodate and osmium tetroxide in tetrahydrofuran and water.

The utility of a compound of the invention or a pharmaceutically acceptable salt thereof (hereinafter, collectively referred to as a "Compound") may be demonstrated by standard 20 tests and clinical studies, including those disclosed in the publications noted above, and those described below.

-20-

SP Receptor Binding Assay (Test A)

The ability of a Compound of the invention to antagonize the binding of SP at the NK1 receptor may be demonstrated using an assay using the human NK1 receptor expressed in Mouse Erythroleukemia (MEL) cells. The human NK1 receptor was isolated and characterized 5 as described in: B. Hopkins, et al. "Isolation and characterization of the human lung NK1 receptor cDNA" Biochem. Biophys. Res. Comm., 1991, 180, 1110-1117; and the NK1 receptor was expressed in Mouse Erythroleukemia (MEL) cells using a procedure similar to that described in Test B below.

10 Neurokinin A (NKA) Receptor Binding Assay (Test B)

The ability of a Compound of the invention to antagonize the binding of NKA at the NK2 receptor may be demonstrated using an assay using the human NK2 receptor expressed in Mouse Erythroleukemia (MEL) cells, as described in: Aharony, D., et al. "Isolation and 15 Pharmacological Characterization of a Hampster Neurokinin A Receptor cDNA" Molecular Pharmacology, 1994, 45, 9-19. In an initial use of this assay, the IC₅₀ measured for the standard compound L-659,877 was found to be 30 nM versus ³H-NKA binding to MEL-membranes.

The selectivity of a Compound for binding at the NK1 and the NK2 receptors may be shown by determining its binding at other receptors using standard assays, for example, 20 one using a tritiated derivative of NKB in a tissue preparation selective for NK3 receptors. In general, the Compounds of the invention which were tested demonstrated statistically significant binding activity in Test A and Test B with a K_i of 1 mM or much less typically being measured. For example, the compound of Example 1 demonstrated a K_i of 163 nanomolar in Test A, and a K_i of 6.81 nanomolar in Test B.

25

Rabbit Pulmonary Artery: NK1 in vitro functional assay (Test C)

The ability of a Compound of the invention to antagonize the action of the agonist Ac-[Arg⁶, Sar⁹, Met(O₂)¹¹] Substance P (6-11), ASMSP, in a pulmonary tissue may be demonstrated as follows.

-21-

Male New Zealand white rabbits are euthanized via i.v. injection into the ear vein with 60 mg/kg Nembutal (50 mg/ml). Preceding the Nembutal into the vein is Heparin (1000 units/ml) at 0.0025 ml/kg for anticoagulant purposes. The chest cavity is opened from the top of the rib cage to the sternum and the heart, lungs and part of the trachea are removed. The 5 pulmonary arteries are isolated from the rest of the tissues and cut in half to serve as pairs. The segments are suspended between stainless steel stirrups, so as not to remove any of the endothelium, and placed in water-jacketed (37.0 °C) tissue baths containing physiological salt solution of the following composition (mM): NaCl, 118.0; KCl, 4.7; CaCl₂, 1.8; MgCl₂, 0.54; NaH₂PO₄, 1.0; NaHCO₃, 25.0; glucose, 11.0; indomethacin, 0.005(to inhibit cyclooxygenase); 10 and dl-Propranolol, 0.001(to block β receptors); gassed continuously with 95% O₂-5% CO₂. Responses are measured on a Grass polygraph via Grass FT-03 transducers.

Initial tension placed on each tissue is 2 grams, which is maintained throughout the 1.0 hour equilibration period. Tissues are washed with the physiological salt solution at 15 minute intervals. At the 30 and 45 minute wash the following treatments are added: 1x10⁻⁶M 15 Thiorphan (to block E.C.3.4.24.11), 3x10⁻⁸M (S)-N-[2-(3,4-Dichloro-phenyl)-4-[4-(2-oxoperhydropyrimidin-1-yl)piperidino]butyl]-N-methylbenzamide (to block NK₂ receptors), and the given concentration of the Compound being tested. At the end of the 1.0 hour equilibration, 3x10⁻⁶M Phenylephrine hydrochloride is added for 1.0 hour. At the end of the 1.0 hour, a dose relaxation curve to ASMSP is done. Each tissue is treated as a individual and is considered 20 finish when it fails to relax further for 2 consecutive doses. When a tissue is complete, 1x10⁻³M Papaverine is added for maximum relaxation.

Percent inhibition is determined when a tested Compound produces a statistically significant ($p<0.05$) reduction of the total relaxation which is calculated using the total relaxation of the Papaverine as 100%. Potencies of the Compounds are determined by 25 calculating the apparent dissociation constants (K_B) for each concentration tested using the standard equation:

$$K_B = [\text{antagonist}] / (\text{dose ratio} - 1)$$

-22-

where dose ratio = antilog[(agonist -log molar EC₅₀ without Compound) - (-log molar EC₅₀ with Compound)]. The K_B values may be converted to the negative logarithms and expressed as -log molar K_B (i.e. pK_B). For this evaluation, complete concentration-response curves for agonist obtained in the absence and presence of the Compound tested using paired pulmonary artery rings. The potency of the agonist is determined at 50% of its own maximum relaxation in each curve. The EC₅₀ values are converted to negative logarithms and expressed as -log molar EC₅₀.

NK2 in vitro functional assay (Test D)

The ability of a Compound of the invention to antagonize the action of the agonist [β-ala⁸] NKA (4-10), BANK, in a pulmonary tissue may be demonstrated as follows.

Male New Zealand white rabbits are euthanized via i.v. injection into the ear vein with 60 mg/kg Nembutal (50 mg/ml). Preceding the Nembutal into the vein is Heparin (1000 units/ml) at 0.0025 ml/kg for anticoagulant purposes. The chest cavity is opened from the top of the rib cage to the sternum and a small incision is made into the heart so that the left and right pulmonary arteries can be cannulated with polyethylene tubing (PE260 and PE190 respectively). The pulmonary arteries are isolated from the rest of the tissues, then rubbed over an intimal surface to remove the endothelium, and cut in half to serve as pairs. The segments are suspended between stainless steel stirrups and placed in water-jacketed (37.0 °C) tissue baths containing physiological salt solution of the following composition (mM): NaCl, 118.0; KCl, 4.7; CaCl₂, 1.8; MgCl₂, 0.54; NaH₂PO₄, 1.0; NaHCO₃, 25.0; glucose, 11.0; and indomethacin, 0.005 (to inhibit cyclooxygenase); gassed continuously with 95% O₂-5% CO₂. Responses are measured on a Grass polygraph via Grass FT-03 transducers.

Initial tension placed on each tissue is 2 grams, which is maintained throughout the 45 minute equilibration period. Tissues are washed with the physiological salt solution at 15 minute intervals. After the 45 minute equilibration period, 3x10⁻²M KCl is given for 60 minutes to test the viability of the tissues. The tissues are then washed extensively for 30 minutes. The concentration of the Compound being tested is then added for 30 minutes. At the end of the 30 minutes, a cumulative dose response curve to BANK is performed. Each tissue is

-23-

treated as a individual and is considered finish when it fails to contract further for 2 consecutive doses. When a tissue is complete, 3×10^{-2} M BaCl₂ is added for maximum contraction.

Percent inhibition is determined when a tested Compound produces a statistically significant ($p < 0.05$) reduction of the total contraction which is calculated using the total contraction of the BaCl₂ as 100%. Potencies of the Compounds are determined by calculating the apparent dissociation constants (K_B) for each concentration tested using the standard equation:

$$K_B = [\text{antagonist}] / (\text{dose ratio} - 1)$$

10

where dose ratio = antilog[(agonist - log molar EC₅₀ without Compound) - (-log molar EC₅₀ with Compound)]. The K_B values may be converted to the negative logarithms and expressed as -log molar K_B (i.e. pK_B). For this evaluation, complete concentration-response curves for agonist obtained in the absence and presence of the Compound tested using paired pulmonary artery rings. The potency of the agonist is determined at 50% of its own maximum relaxation in each curve. The EC₅₀ values are converted to negative logarithms and expressed as -log molar EC₅₀.

NK₁ and NK₂ in vivo functional assay (Test E)

20

The activity of a compound as an antagonist of NK₁ and/or NK₂ receptors also may be demonstrated in vivo in laboratory animals as described in: Buckner et al. "Differential Blockade by Tachykinin NK₁ and NK₂ Receptor Antagonists of Bronchoconstriction Induced by Direct-Acting Agonists and the Indirect-Acting Mimetics Capsaicin, Serotonin and 2-Methyl-Serotonin in the Anesthetized Guinea Pig." *J. Pharm. Exp. Ther.*, 1993, Vol 267(3), pp 1168-

25

1175. The assay is carried out as follows.

Compounds are tested in anesthetized guinea pigs pretreated with i.v. indomethacin (10 mg/kg, 20 min.), propranolol (0.5 mg/kg, 15 min.), and thiophan (10 mg/kg, 10 min). Antagonists or vehicle are administered i.v. and orally, 30 and 120 minutes prior to increasing concentrations of agonist, respectively. The agonists used in these studies are ASMSM

- 24 -

(Ac-[Arg⁶,Sar⁹,Met(O₂)¹¹]-SP(6-11)) and BANK (β -ala-8 NKA4-10). Administered i.v., ASMSP is selective for NK₁ receptors, and BANK is selective for NK₂ receptors. Maximum response is defined as zero conductance (G_L , 1/R_p). ED₅₀ values are calculated (the dose of agonist resulting in a reduction of G_L to 50% of baseline), and converted to the negative logarithm (-logED₅₀). Data are expressed as mean \pm SEM and statistical differences were determined using ANOVA/Tukey-Kramer and Student's t-test, with p < 0.05 considered statistically significant.

Clinical Studies

10 Clinical studies to demonstrate the efficacy of a Compound of the invention may be carried out using standard methods. For example, the ability of a Compound to prevent or treat the symptoms of asthma or asthma-like conditions may be demonstrated using a challenge of inhaled cold air or allergen and evaluation by standard pulmonary measurements such as, for example, FEV₁ (forced expiratory volume in one second) and FVC (forced vital capacity),
15 analyzed by standard methods of statistical analysis.

It will be appreciated that the implications of a Compound's activity in the above described Tests is not limited to asthma, but rather, that the Tests provide evidence of general antagonism of both SP and NKA.

SP and NKA have been implicated in the pathology of numerous diseases
20 including: rheumatoid arthritis, Alzheimer's disease, oedema, allergic rhinitis, inflammation pain, gastrointestinal-hypermotility, anxiety, emesis, Huntington's Disease, Psychoses, hypertension, migraine, bladder hypermotility and urticaria. Accordingly, one feature of the invention is the use of a compound of formula I or a pharmaceutically acceptable salt thereof in the treatment of a disease in a human or other mammal in need thereof in which SP or NKA is implicated and
25 antagonism of its action is desired.

Asthma is characterized by both chronic inflammation and hyperresponsiveness of the airways. The NK1 receptor is known to mediate inflammation and mucus hypersecretion in airways; and the NK2 receptor is involved in the control of the tone of bronchial smooth muscle. Thus, agents capable of antagonizing the actions of SP and NKA, at the NK1 and NK2 receptors, respectively, are capable of reducing both the chronic inflammation and the airway

hyperresponsiveness which are symptomatic of asthma. It has been suggested that an antagonist having mixed affinity for NK1 and NK2 could be therapeutically superior to a receptor selective antagonist. C.M. Maggi "Tachykinin Receptors and Airway Pathophysiology" EUR. Respir. J., 1993, 6, 735-742 at 739. Also, it has been suggested that a synergistic effect against 5 bronchoconstriction may result from the simultaneous application of an NK1 antagonist and an NK2 antagonist. D.M. Foulon, et al. "NK1 and NK2 Receptors Mediated Tachykinin and Resiniferatoxin-induced Bronchospasm in Guinea Pigs" American Review of Respiratory Disease, 1993, 148, 915-921. Accordingly, another feature of the invention is the use of a compound of formula I or a pharmaceutically acceptable salt thereof in the treatment of asthma 10 in a human or other mammal in need thereof.

Because of the range of effects attributable to the actions of SP and NKA, compounds which are capable of blocking their actions may also be useful as tools for further evaluating the biological actions of other neurotransmitters in the Tachykinin family. As a 15 result, another feature of the invention is provided by the use of a compound of formula I or a salt thereof as a pharmacological standard for the development and standardization of new disease models or assays for use in developing new therapeutic agents for treating diseases in which SP or NKA are implicated or for assays for their diagnosis.

When used in the treatment of a disease, a compound of the invention is generally administered as an appropriate pharmaceutical composition which comprises a compound of 20 formula I or a pharmaceutically acceptable salt thereof as defined hereinbefore and a pharmaceutically acceptable diluent or carrier, the composition being adapted for the particular route of administration chosen. Such a composition is provided as a further feature of the invention. It may be obtained employing conventional procedures and excipients and binders, and it may be one of a variety of dosage forms. Such forms include, for example, tablets, 25 capsules, solutions or suspensions for oral administration; suppositories for rectal administration; sterile solutions or suspensions for administration by intravenous or intramuscular infusion or injection; aerosols or nebulizer solutions or suspensions for administration by inhalation; or powders together with pharmaceutically acceptable solid diluents such as lactose for administration by insufflation.

For oral administration a tablet or capsule containing up to 250 mg (and typically 30 5 to 100 mg) of a compound of formula I may conveniently be used. For administration by

inhalation, a compound of formula I will be administered to humans in a daily dose range of, for example, 5 to 100 mg, in a single dose or divided into two to four daily doses. Similarly, for intravenous or intramuscular injection or infusion a sterile solution or suspension containing up to 10% w/w (and typically 0.05 to 5% w/w) of a compound of formula I may conveniently be used.

5

The dose of a compound of formula I to be administered will necessarily be varied according to principles well known in the art taking account of the route of administration and the severity of the condition and the size and age of the patient under treatment. However, in general, the compound of formula I will be administered to a warm-blooded animal (such as man) so that a dose in the range of, for example, 0.01 to 25 mg/kg (and usually 0.1 to 5 mg/kg) is received. It will be understood that generally equivalent amounts of a pharmaceutically acceptable salt of a compound of formula I may be used.

10

The invention will now be illustrated by the following non-limiting examples in which, unless stated otherwise:

15

(i) temperatures are given in degrees Celsius (°C); operations were carried out at room or ambient temperature, that is, at a temperature in the range of 18-25 °C;

(ii) organic solutions were dried over anhydrous magnesium sulfate; evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 pascals; 4.5-30 mm Hg) with a bath temperature of up to 60 °C;

20

(iii) chromatography means flash chromatography on silica gel; thin layer chromatography (TLC) was carried out on silica gel plates;

(iv) in general, the course of reactions was followed by TLC and reaction times are given for illustration only;

25

(v) melting points are uncorrected and (dec) indicates decomposition; the melting points given are those obtained for the materials prepared as described; polymorphism may result in isolation of materials with different melting points in some preparations;

(vi) final products had satisfactory proton nuclear magnetic resonance (NMR) spectra;

30

(vii) yields are given for illustration only and are not necessarily those which may be obtained by diligent process development; preparations were repeated if more material was required;

-27-

(viii) when given, NMR data is in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard, determined at 300 MHz using deuterated chloroform (CDCl_3) as solvent; conventional abbreviations for signal shape are used; for AB spectra the directly observed shifts are reported;

5 coupling constants (J) are given in Hz; Ar designates an aromatic proton when such an assignment is made;

(ix) chemical symbols have their usual meanings; SI units and symbols are used;

(x) reduced pressures are given as absolute pressures in pascals (Pa); elevated pressures are given as gauge pressures in bars;

10 (xi) solvent ratios are given in volume:volume (v/v) terms; and

(xii) Mass spectra (MS) were run using an automated system with atmospheric pressure chemical ionization (APCI). Methanol mobile phase enters the probe where it is pneumatically converted into an aerosol and rapidly heated into the gas phase at the probe tip. Hot gas from the probe enters the heated volume of the source which contains the corona discharge pin typically maintained at 3 kV. Methanol molecules rapidly react with ions from the corona discharge to produce stable reagent ions. Analyte molecules introduced into the mobile phase react with the reagent ions at atmospheric pressure and typically become protonated (for positive ions) or deprotonated (for negative ions). Where indicated, the following alternative methods of ionization were used: a) desorption chemical ionization (CI) using methane reagent gas and a direct exposure probe; b) electron impact (EI) or c) fast atom bombardment (FAB). Generally, only spectra where parent masses are observed are reported.

-28-

Example 1. N-Benzyl-3-(4-acetamido-4-phenylpiperidino)-1-(3,4-dichlorophenyl)propyl carbamate.

Benzylisocyanate (25 uL) was added to the alcohol from b below (75 mg), in tetrahydrofuran (1.0 mL). After 2 hours, additional benzylisocyanate (5 microliters), was added 5 and the mixture stirred for 1 hour. The solvents were evaporated and the residue purified by chromatography, with methanol:dichloromethane (5:95) as the eluent, to give the title compound as a white foam (63 mg); MS (APCI) m+H+554. Analysis for C₃₀H₃₃N₃O₃Cl₂•0.25 H₂O: Calculated: C, 64.46; H, 6.04; N, 7.52; Found: C, 64.24, H, 5.99, N, 7.52.

The intermediate alcohol was prepared as follows.

a. 3-(4-Acetamido-4-phenylpiperidino)-1-(3,4-dichlorophenyl)propanone hydrochloride salt. Hydrochloric acid (1.32 mL, 6.25 N) was added to 4-acetamido-4-phenylpiperidine (1.73 g). Formalin (0.525 mL) was added and the resulting solution was allowed to stir overnight. Acetic anhydride (3.4 mL) was added and the solution was heated to reflux for 75 minutes. 3,4-dichloroacetophenone was added and the mixture was allowed to reflux overnight. 15 The solvent was evaporated and the residual solid was suspended in acetone, collected by filtration, rinsed with acetone, and dried in vacuo to afford the ketone as the hydrochloride salt (2.52 g). This material was used directly in sub-part b, without further purification.

b. 3-(4-Acetamido-4-phenylpiperidino)-1-(3,4-dichlorophenyl)-1-propanol.

The ketone from sub-part a (530 mg) was suspended in ethanol (4 mL). An equal volume of 20 tetrahydrofuran was added, followed by sodium borohydride (100 mg). After 4 hours, water was added and the solvent was evaporated. The residue was partitioned between diethyl ether and water. The ether phase was washed (saturated brine), dried (anhydrous sodium sulfate), filtered, and evaporated to give an oil. Chromatography, with dichloromethane:methanol (20:1) as the eluent gave the alcohol as a white foam (0.31 g).

25

Example 2. N-((S)-a-Methylbenzyl)-3-(4-acetamido-4-phenylpiperidino)-1-(3,4-dichlorophenyl)propyl carbamate.

Using a procedure similar to that described in Example 1, except replacing the benzylisocyanate used therein with (S)-(-)-*a*-methylbenzyl isocyanate, the title compound was prepared; MS (APCI) m+H=568.

5 **Example 3.** N-(2-Methoxybenzyl)-N-methyl-N'-[1-(S)-(3,4-dichlorophenyl)-
3-(4-(2-(S)-methylsulfinylphenyl)-piperidino)propyl] urea.

The aldehyde from sub-part b below (0.250 g) was dissolved in tetrahydrofuran (1 mL). 4-(2-(S)-Methyl-sulfinylphenyl)piperidine (0.169 g) was added followed by acetic acid (0.055 g). Methanol (8 mL) was added followed by sodium cyanoborohydride (0.051 g). After 10 hours the mixture was concentrated and the residue partitioned between ethyl acetate (50 mL) and saturated aqueous NaHCO₃ (20 mL). The organic phase was separated, extracted with brine (20 mL), dried (Na₂SO₄), filtered, and evaporated. The residue was purified by chromatography with dichloromethane:methanol (95:5) as the eluent to give the title compound as a white solid (0.175 g). MS(APCI): m+H=602. Analysis for C₃₁H₃₇Cl₂N₃O₃S•0.5 H₂O: Calculated: C, 60.88; H, 6.26; N, 6.87; Found: C, 61.05; H, 6.27; N, 7.14;

The intermediate N-(2-Methoxybenzyl)-N-methyl-N'-[1-(S)-(3,4-dichlorophenyl)-3-oxopropyl] urea was prepared as follows.

20 a. N-(2-Methoxybenzyl)-N-methyl-N'-[1-(S)-(3,4-dichlorophenyl)-3-butenyl] urea.
2-(S)-(3,4-dichloro-phenyl)-4-pentenoic acid (1.22 g) was dissolved in toluene (60 mL) under nitrogen. Triethylamine (0.51 g) was added followed by diphenylphosphoryl azide (1.38 g). The mixture was heated at 100 °C for 16 hours, cooled to room temperature, and N-methyl-2-methoxybenylamine (1.00 g) was added. After 2 hours the reaction was diluted with HCl (50 mL, 1N) and ethyl acetate (50 mL). The organic phase was separated, and extracted with saturated aqueous NaHCO₃ (25 mL), and with brine (25 mL). The organic phase was dried (Na₂SO₄), filtered and evaporated. The residue was purified by chromatography with hexane:ethyl acetate (4:1) as the eluent to afford the urea as a yellow oil (1.40 g). MS(APCI): m+H=393.

- 30 -

b. N-(2-Methoxybenzyl)-N-methyl-N'-[1-(S)-(3,4-dichlorophenyl)-3-oxopropyl] urea. The material from sub-part a above (1.39 g) was dissolved in tetrahydrofuran (30 mL) and water (10 mL). Osmium tetroxide (0.01 g) was added. Sodium periodate (1.63 g) was added gradually in portions over 10 minutes. After 3 hours the reaction was diluted with water (20 mL) and saturated aqueous NaHCO₃ (20 mL), and extracted with ethyl ether (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried (Na₂SO₄), filtered, and evaporated. The residue was purified by filtration through a florisil plug, to give the aldehyde as a colorless oil (0.75 g). MS(APCI): m+H=395.

10

The intermediate 4-(2-(S)-methylsulfinylphenyl)piperidine was prepared as described in International Patent Application Publication Number WO 95/16682, Example 68, sub-parts a and b. The absolute configuration of the sulfoxide center is (S).

Examples 4-5

15 Using a procedure similar to that described in Example 3, except replacing the 4-(2-methylsulfinylphenyl)piperidine used therein with the requisite piperidine, the following compounds of formula I wherein Q² is 3,4-dichlorophenyl, Q³ is hydrogen, Q⁴ is 3-(2-methoxybenzyl)-3-methylureido and Q¹ has the indicated value were prepared. The compounds of Examples 4 and 5 were prepared as the (S) enantiomer at the center marked by * in formula I.

20 **Example 4.** Q¹=4-Acetamido-4-phenylpiperidino; MS(APCI): m+H=597. Analysis for C₃₂H₃₈Cl₂N₄O₃•0.4 H₂O: Calculated: C, 63.55; H, 6.47; N, 9.26; Found: C, 63.64; H, 6.47; N, 9.22.

25 **Example 5.** Q¹=4-(2-(Oxoperhydropyrimidinyl)-piperidino; MS(APCI): m+H=562. Analysis for C₂₈H₃₇Cl₂N₅O₃•0.4 H₂O: Calculated: C, 59.03; H, 6.69; N, 12.29; Found: C, 59.01; H, 6.61; N, 12.26.

Examples 6-12

Using a procedure similar to that described in Example 3, except replacing the 4-(2-methylsulfinylphenyl)piperidine used therein with the requisite piperidine, the following compounds of formula I wherein Q² is 3,4-dichlorophenyl, Q³ is hydrogen, Q⁴ is 3-indan-1-ylureido and Q¹ has the indicated value were prepared. The compounds were prepared as the (S) enantiomer at the center marked by * in formula I.

Example 6. Q¹=4-Hydroxy-4-phenylpiperidino; MS(APCI): m+H=538

Example 7. Q¹=4-Carbamoyl-4-piperidinopiperidino; MS(APCI): m+H=572

Example 8. Q¹=4-(2-Oxopiperidino)-4-(N-methylcarbamoyl)piperidino;

MS(APCI): m+H=600

Example 9. Q¹=4-(2-Oxopiperidino)piperidino; MS(APCI): m+H=543

Example 10. Q¹=4-(2-(S)-methylsulfinylphenyl)piperidino; MS(APCI): m+H=584

Example 11. Q¹=4-(2-Oxo-2,3-dihydrobenzimidazol-1-yl)piperidino; MS(APCI): m+H=578

Example 12. Q¹=4-Acetamido-4-phenylpiperidino; MS(APCI): m+H=579

Example 13. Q¹=4-(4-Methylsulfinylphenyl)piperidino; MS(APCI): m+H=584.

The intermediate (S)-3-(3,4-dichlorophenyl)-3-(3-indan-1-ylureido)propanal, used to prepare the compounds of Examples 6-13, was prepared using a sequence similar to that described in Example 3, sub-parts a and b, by substituting 1-aminoindan for N-methyl-2-methoxybenzylamine in sub-part a; MS(APCI): m+H=377.

Examples 14-20

Using a procedure similar to that described in Example 3, except replacing the 4-(2-methylsulfinylphenyl)piperidine used therein with the requisite piperidine, the following compounds of formula I wherein Q² is 3,4-dichlorophenyl, Q³ is hydrogen, Q⁴ is 3-(2-methoxybenzyl)-3-methylureido and Q¹ has the indicated value were prepared. The compounds were prepared as the (S) enantiomer at the center marked by * in formula I.

- 32 -

Example 14. $Q^1=4\text{-Carbamoyl-4-(dimethylamino)piperidino}$; MS(APCI);
m+H=550.

Example 15. $Q^1=4\text{-Carbamoyl-4-piperidinopiperidino}$; MS(APCI); m+H=590.

Example 16. $Q^1=4\text{-(2-Oxopiperidino)-4-(N-methylcarbamoyl)piperidino}$;

5 MS(APCI); m+H=618

Example 17. $Q^1=4\text{-}(2\text{-Oxopiperidino)piperidino}$; MS(APCI); m+H=561

Example 18. $Q^1=4\text{-(4-Methylsulfinylphenyl)piperidino}$; MS(APCI); m+H=602

Example 19. $Q^1=4\text{-(2-Oxo-2,3-dihydrobenzimidazol-1-yl)piperidino}$; MS(APCI);
m+H=596.

10 **Example 20.** $Q^1=4\text{-Hydroxy-4-phenylpiperidino}$; MS(APCI); m+H=556.

Examples 21-30

Using a procedure similar to that described in Example 3, except replacing the
4-(2-methylsulfinylphenyl)piperidine used therein with the requisite piperidine, the following
15 compounds of formula I wherein Q^2 is 3,4-dichlorophenyl, Q^3 is hydrogen, Q^4 is 2-methoxyphenethylcarbonylamino and Q^1 has the indicated value were prepared. The
compounds were prepared as the (S) enantiomer at the center marked by * in formula I.

Example 21. $Q^1=4\text{-Hydroxy-4-phenylpiperidino}$; MS(APCI); m+H=541.

20 **Example 22.** $Q^1=4\text{-Carbamoyl-4-(dimethylamino)piperidino}$; MS(APCI);
m+H=535.

Example 23. $Q^1=4\text{-Carbamoyl-4-piperidinopiperidino}$; MS(APCI); m+H=575.

Example 24. $Q^1=4\text{-(2-Oxopiperidino)-4-(N-methylcarbamoyl)piperidino}$;
MS(APCI); m+H=603.

25 **Example 25.** $Q^1=4\text{-(2-Oxopiperidino)piperidino}$; MS(APCI); m+H=546.

Example 26. $Q^1=4\text{-(4-Methylsulfinylphenyl)piperidino}$; MS(APCI); m+H=587.

Example 27. $Q^1=4\text{-(2-(S)-Methylsulfinylphenyl)piperidino}$; MS(APCI);
m+H=587.

- 33 -

Example 28. Q¹=4-(2-Oxo-2,3-dihydrobenzimidazol-1-yl)piperidino; MS(APCI): m+H=581.

Example 29. Q¹=4-(2-Oxoperhydropyrimidin-1-yl)piperidino; MS(APCI): m+H=547.

5 **Example 30.** Q¹=4-Acetamido-4-phenylpiperidino; MS(APCI): m+H=582.

The intermediate (S)-3-(3,4-dichlorophenyl)-3-(2-methoxyphenethylcarbonyl-amino)propanal, used to prepare the compounds of Examples 21-30 was prepared as follows.

10 a. (S)-4-(3,4-Dichlorophenyl)-4-(tert-butoxycarbonylamino)-1-butene: (S)-2-(3,4-dichlorophenyl)-4-pentenoic acid (5.00g) was dissolved in 2-methyl-2-propanol (75mL) under nitrogen. Diphenylphosphoryl azide (5.61g) was added followed by triethylamine (2.06g). The reaction mixture was heated at 60°C for 1hour, and at 80°C for 48hours. The mixture was cooled to room temperature, diluted with water (150 mL), and extracted with ethyl acetate (3 x 150 mL). The organic extracts were combined, washed with aqueous HCl (100mL, 1N), saturated aqueous NaHCO₃ (100mL), and brine (100 mL). The organic phase was dried (Na₂SO₄), filtered and evaporated to afford the tert-butyl carbamate as a colorless oil (4.12 g); MS(APCI) : (m+H=316).

20 b. (S)-4-(3,4-dichlorophenyl)-4-(2-methoxyphenethylcarbonylamino)-1-butene. The material from sub-part a above was dissolved in dichloromethane (25 mL), cooled to 0°C, and trifluoroacetic acid (20 mL) was added dropwise. After 30 minutes the mixture was evaporated. The resulting red oil was dissolved in dichloromethane (5 mL) and added to a dichloromethane (50 mL) solution of 3-(2-methoxyphenyl)propionyl chloride at 0°C under nitrogen, and 25 triethylamine (3.00 g) was added. The reaction mixture was stirred overnight at room temperature, diluted with ether (150 mL) and extracted with aqueous HCl (100mL, 1N), saturated aqueous NaHCO₃ (100mL), and brine (100 mL). The organic phase was dried (Na₂SO₄), filtered and evaporated. The residue was purified by chromatography with hexane:ethyl acetate (4:1) as the eluent to give the amide (3.26g); MS(APCI): m+H= 378.

- 34 -

c. (S)-3-(3,4-dichlorophenyl)-3-(2-methoxyphenethylcarbonylamino)propanal. The material from sub-part b above (3.00 g) was dissolved in tetrahydrofuran (75mL) and water (10mL). Osmium tetroxide (0.02g) was added. Sodium periodate (3.54g) was added gradually in portions over 20 minutes. After 3 hours the reaction was diluted with water (100mL), and extracted with ethyl ether (3x 150mL). The combined organic extracts were washed (aqueous NaHCO₃, brine), dried (Na₂SO₄), filtered, and evaporated. The residue was purified by chromatography with hexane:ethyl acetate (2:1) as the eluent to give the aldehyde (2.10g); MS(APCI): m+H= 380.

Examples 31-40

Using a procedure similar to that described in Example 3, except replacing the 4-(2-methylsulfinylphenyl)piperidine used therein with the requisite piperidine, the following compounds of formula I wherein Q² is 3,4-dichlorophenyl, Q³ is hydrogen, Q⁴ is 2-methoxybenzyloxycarbonylamino and Q¹ has the indicated value were prepared. The compounds were prepared as the (S) enantiomer at the center marked by * in formula I.

Example 31. Q¹=4-Hydroxy-4 phenylpiperidino; MS(APCI): m+H=543.

Example 32. Q¹=4-Carbamoyl-4-(dimethylamino)piperidino; MS(APCI): m+H=537.

Example 33. Q¹=4-Carbamoyl-4-piperidinopiperidino; MS(APCI): m+H=577.

Example 34. Q¹=4-(2-Oxopiperidino)-4-(N-methylcarbamoyl)piperidino;

MS(APCI): m+H=605.

Example 35. Q¹=4-(2-Oxopiperidino)piperidino; MS(APCI): m+H=548.

Example 36 Q¹=4-(4-Methylsulfinylphenyl)piperidino; MS(APCI): m+H=589.

Example 37. Q¹=4-(2-(S)-Methylsulfinylphenyl)piperidino; MS(APCI) m+H=589.

Example 38. Q¹=4-(2-Oxo-2,3-dihydrobenzimidazol-1-yl)piperidino; MS(APCI): m+H=583.

Example 39. Q¹=4-(2-Oxoperhydropyrimidin-1-yl)piperidino; MS(APCI): m+H=549.

- 35 -

Example 40. Q¹=4-Acetamido-4-phenylpiperidino; MS(APCI): m+H=584.

The intermediate is (S)-3-(3,4-dichlorophenyl)-3-(2-methoxybenzyloxycarbonyl-amino)propanal, used to prepare the compounds of Examples 31-40 was prepared as follows.

5

a. (S)-4-(3,4-dichlorophenyl)-4-(2-methoxybenzyloxycarbonylamino)-1-butene. 2-(S)-(3,4-dichlorophenyl)-4-pentenoic acid (1.22 g) was dissolved in toluene (100 mL) under nitrogen. Diphenylphosphoryl azide (5.61 g) was added followed by triethylamine (2.06 g). The mixture was kept at room temperature for 30 minutes, heated at 60°C for 1 hour, and heated at 10 80°C for 2 hours. The mixture was cooled to room temperature. 2-Methoxybenzyl alcohol (5.63 g) was added, and the mixture was heated at 80°C for 72 hours. The mixture was cooled and diluted with water (100 mL) and ethyl acetate (100 mL). The organic phase was separated, and the aqueous phase extracted with additional ethyl acetate (2 x 100 mL). The combined organic extracts were washed with aqueous HCl (100 mL, 1N), saturated aqueous NaHCO₃ (100 mL), and with brine (100 mL). The organic phase was dried (Na₂SO₄), filtered and evaporated. The residue was purified by crystallization from ether-hexane to give the carbamate as a white solid (6.15 g); MS(APCI): m+H= 380.

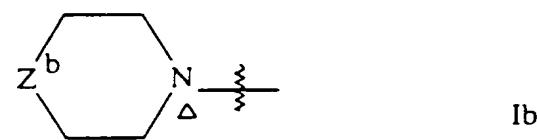
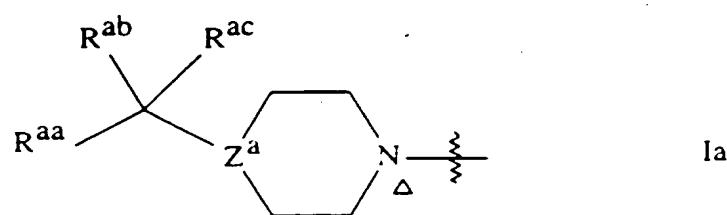
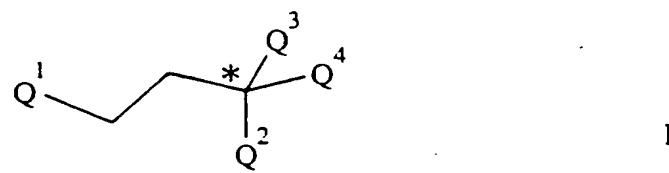
b. (S)-3-(3,4-Dichlorophenyl)-3-(2-methoxybenzyloxycarbonylamino)propanal.
20 The material from sub-part a above (6.05 g) was dissolved in tetrahydrofuran (75 mL) and water (25 mL). Osmium tetroxide (0.04 g) was added. Sodium periodate (7.15 g) was added gradually in portions over 20 minutes. After 3 hours the reaction was diluted with water (100 mL) and extracted with ether (3x 150mL). The combined organic extracts were washed with saturated aqueous NaHCO₃ (150mL), and brine (150 mL), dried (Na₂SO₄), filtered, and evaporated. The residue was purified by filtration through a florisil plug, to give the aldehyde as a foamy solid (5.22 g); MS(APCI): m+H=382.

Example 41. 3-(4-Acetamido-4-phenylpiperidino)-1-(3,4-dichlorophenyl)propyl 3-phenylpropionate.

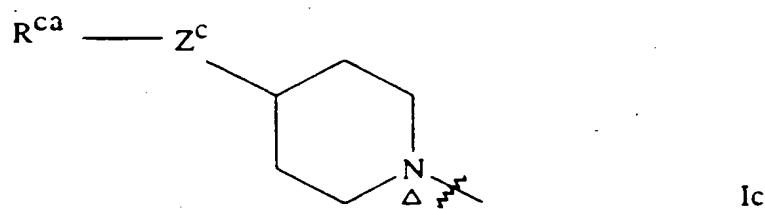
- 36 -

3-Phenylpropionylchloride (21 mg) and triethylamine (13 mg) were added to the alcohol (50 mg) from Example 1 sub-part b in dichloromethane (3 mL) under nitrogen. The mixture was stirred 2 hours at room temperature, and was diluted with saturated aqueous NaHCO₃ (10 mL) and ethyl acetate (10 mL). The organic phase was separated, washed with brine (5 mL), dried (Na₂SO₄), filtered and evaporated. The resulting yellow oil was converted to its hydrochloride salt by treating a dichloromethane (5 mL) solution with dry hydrogen chloride (0.2 mL x 1N in ether) for 10 minutes at room temperature. Evaporation gave a solid which was purified by trituration with ether to give the title compound as a white solid (40 mg); MS(APCI): m+H=553.

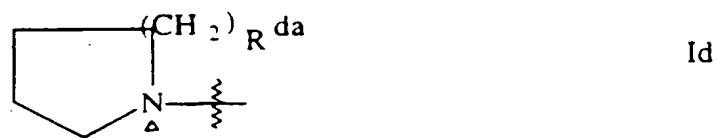
- 37 -



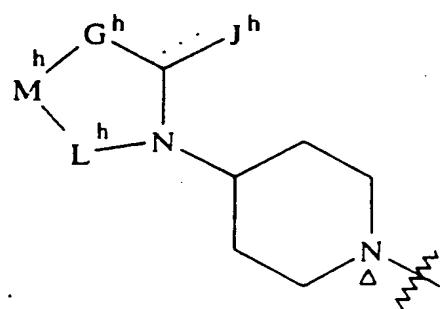
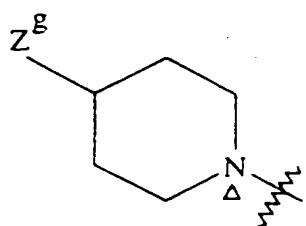
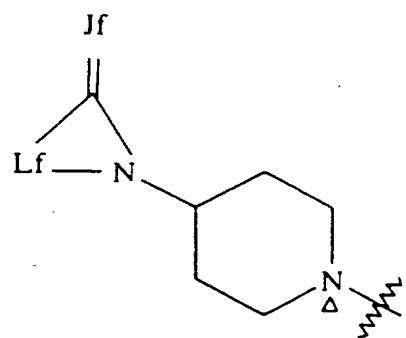
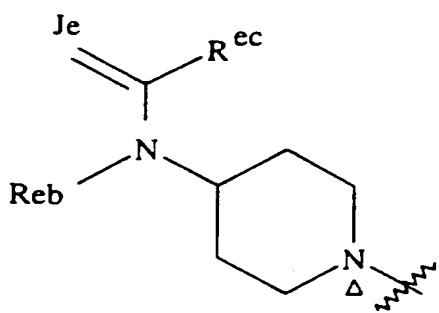
5



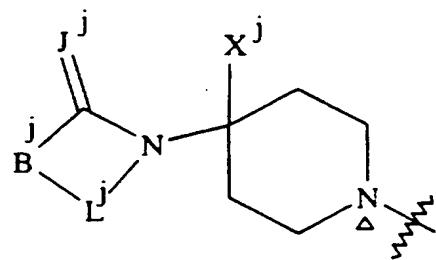
10



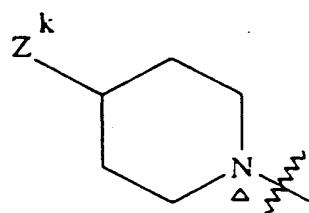
- 38 -



- 39 -

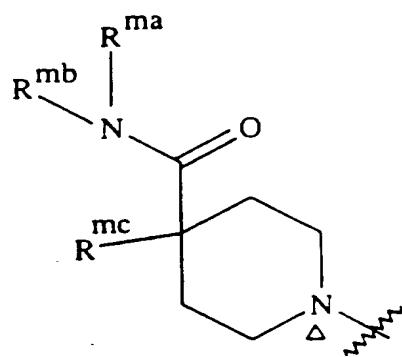


Ij



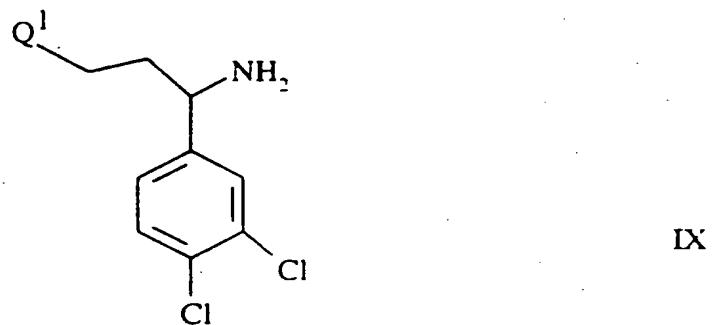
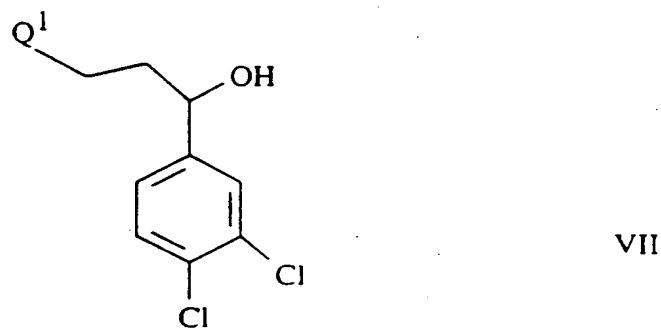
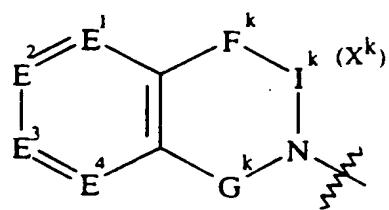
Ik

5

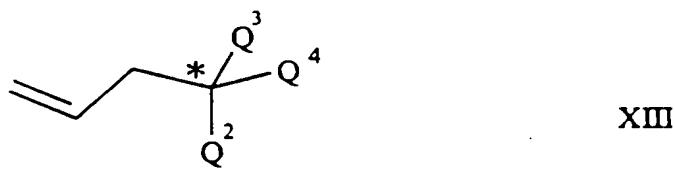


Im

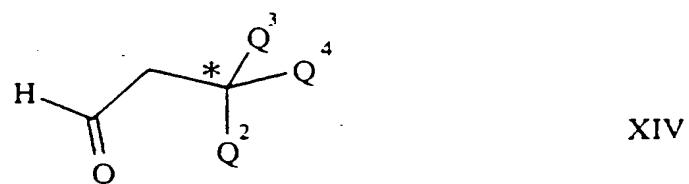
- 40 -



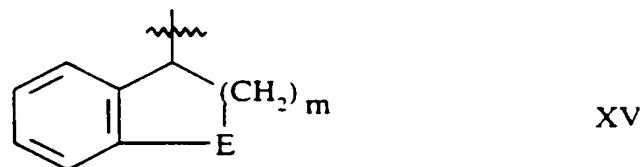
- 41 -



XIII



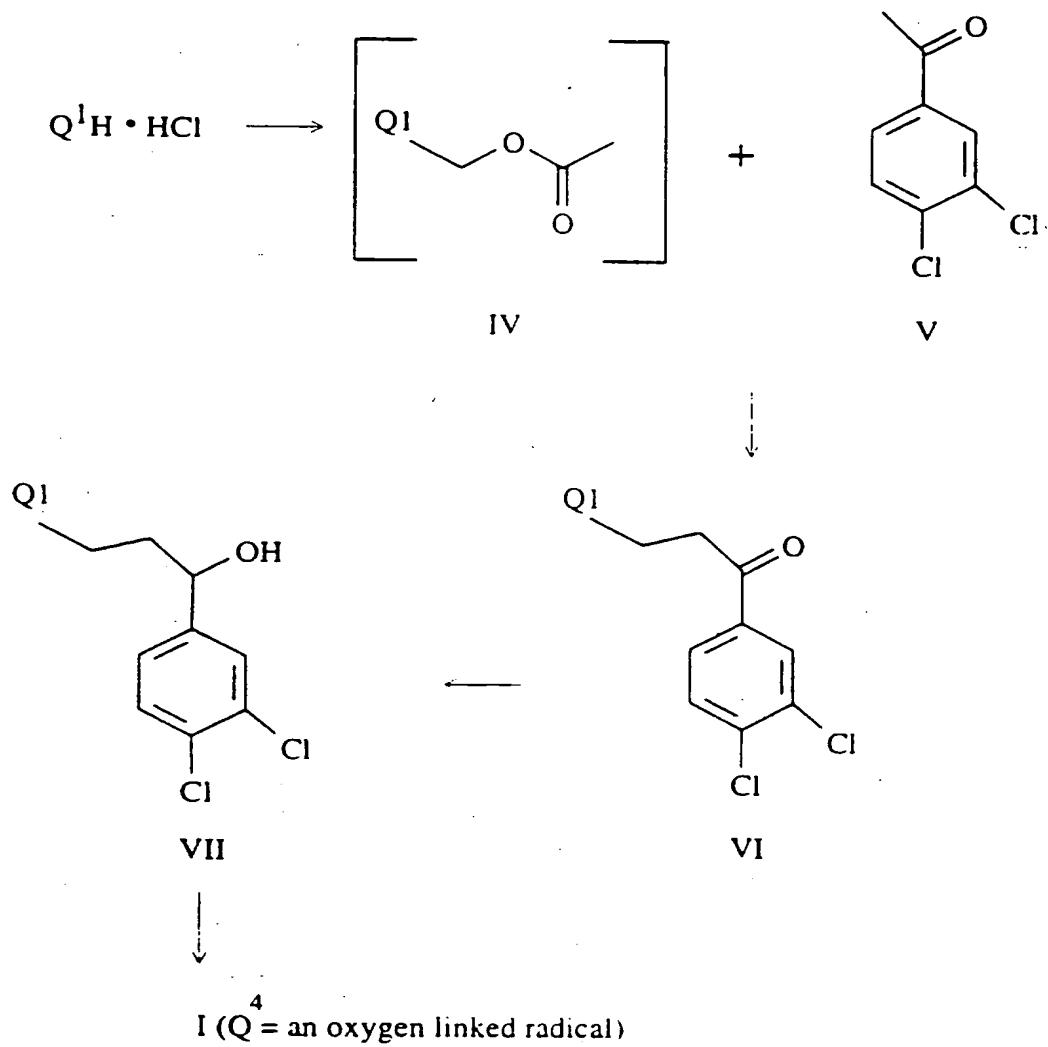
XIV



XV

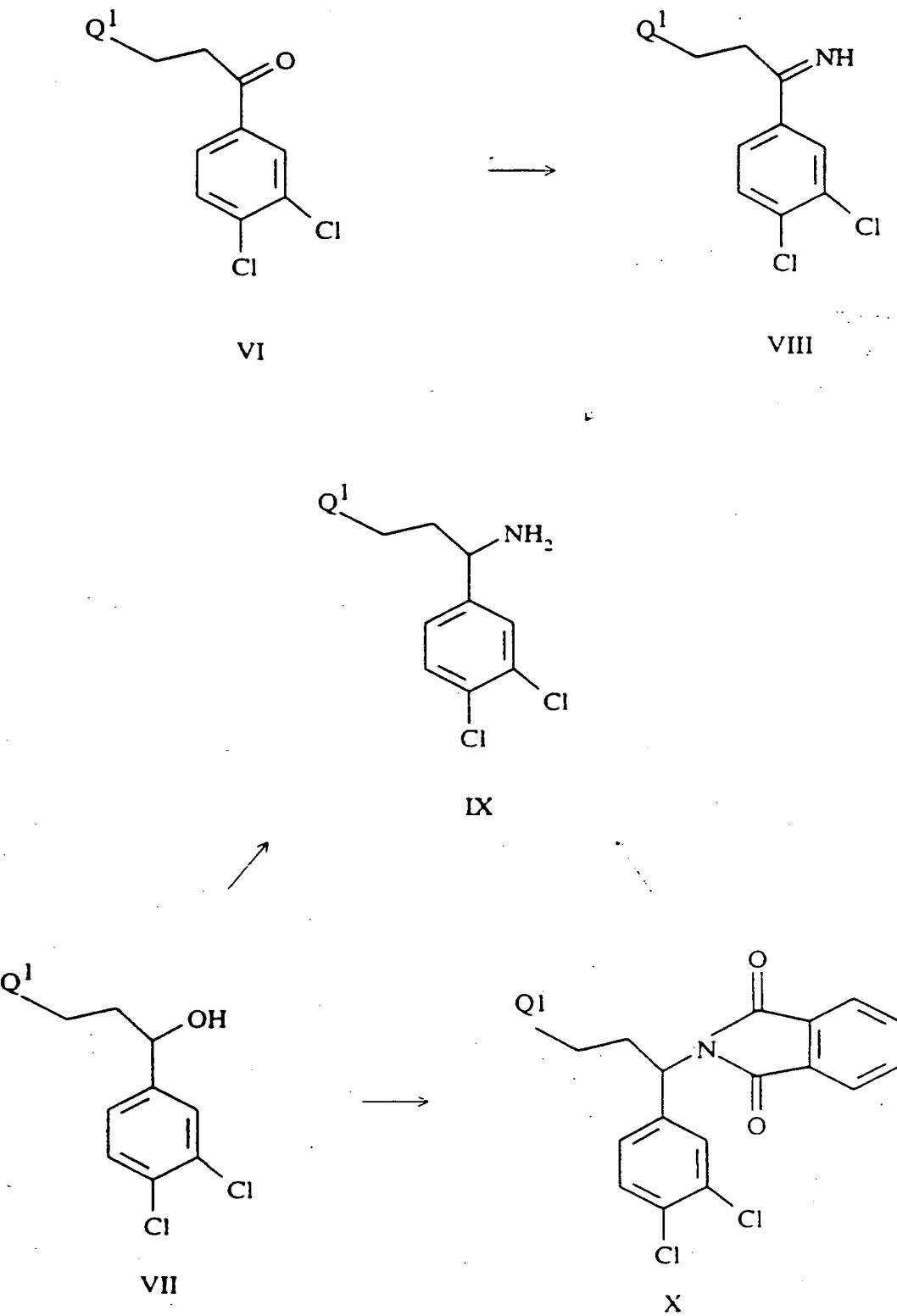
- 42 -

Scheme I



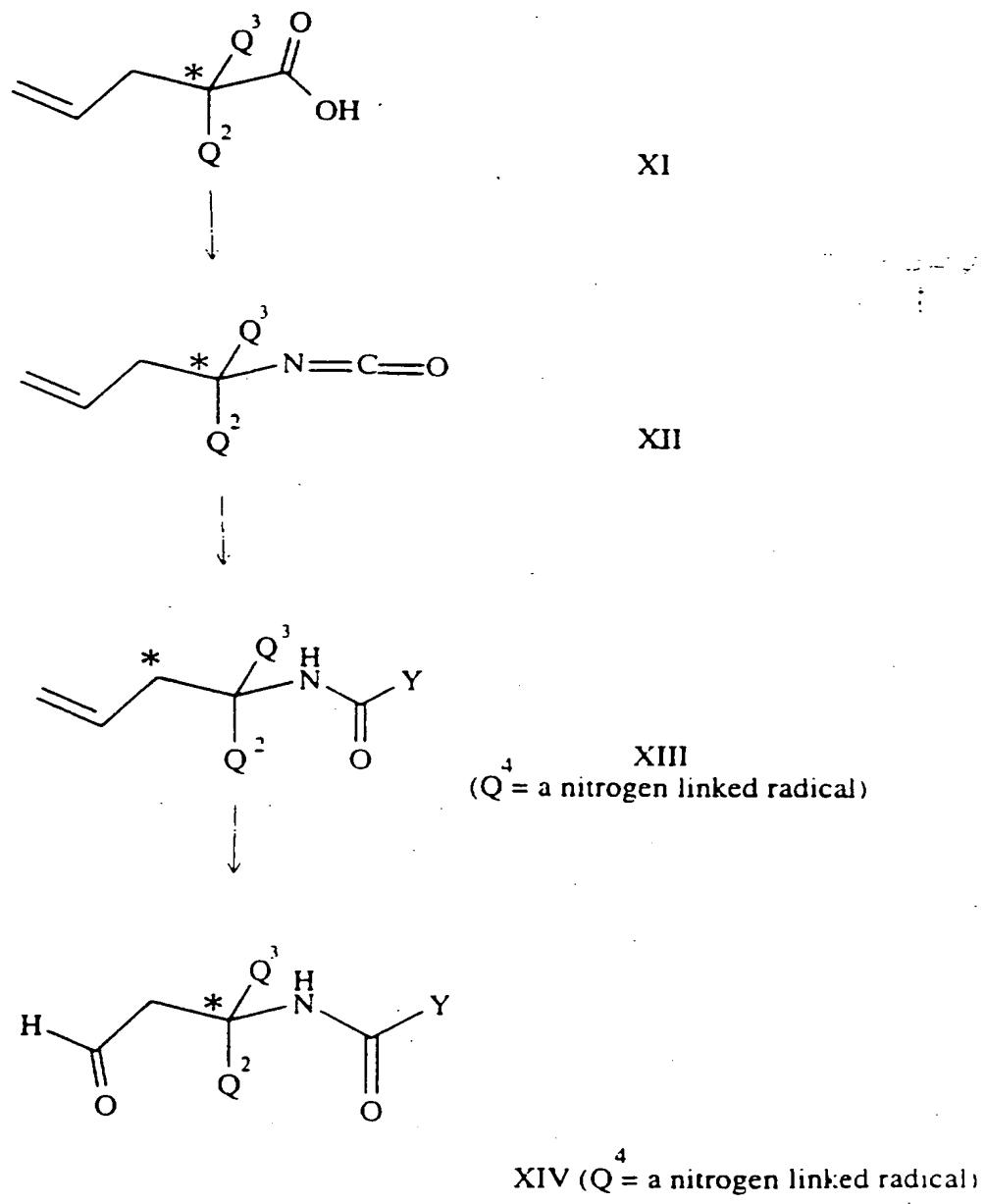
- 43 -

Scheme II



- 44 -

Scheme III

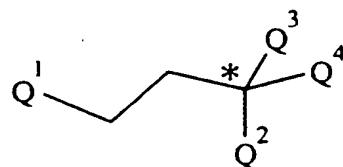


- 45 -

What is claimed is:

1. A compound of formula I:

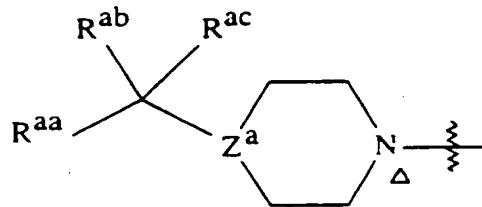
5



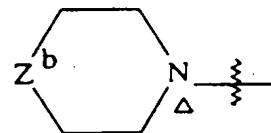
I

wherein

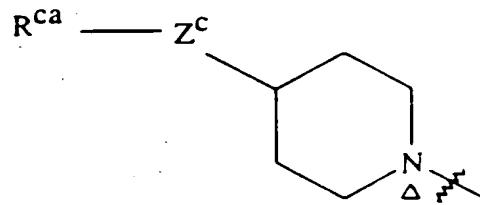
Q^1 is a radical selected from the group of radicals of formulae Ia, Ib, Ic, Id, Ie, If, Ig,
10 Ih, Ij, Ik and Im:



Ia



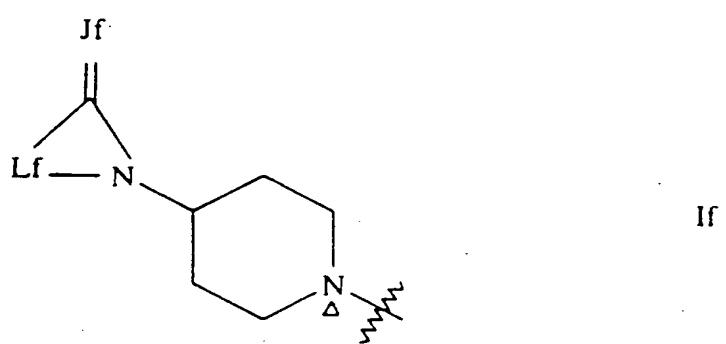
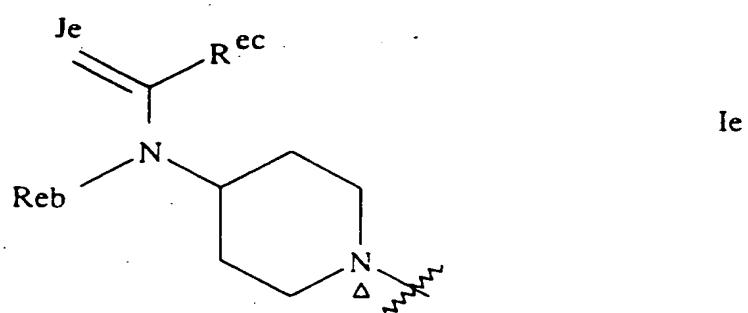
Ib



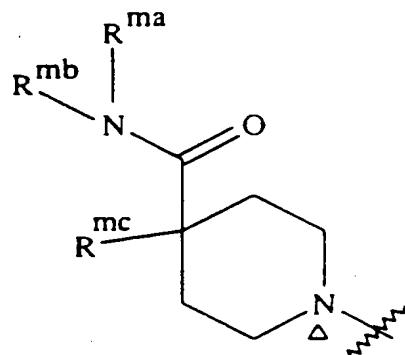
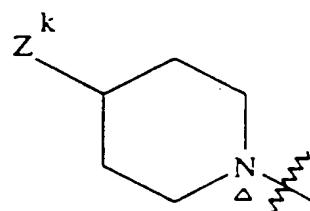
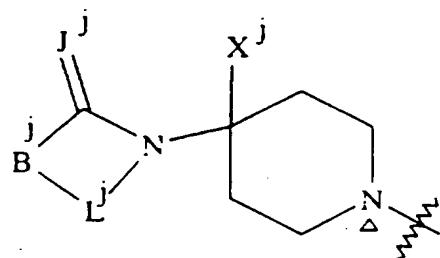
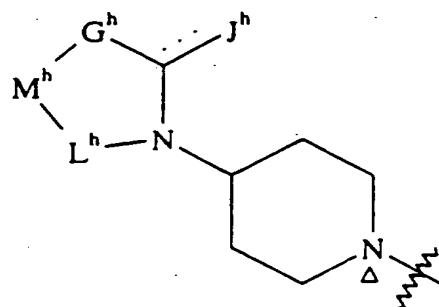
Ic

15

- 46 -



- 47 -



5 wherein

for a radical of formula I^a, Z^a is nitrogen or a group CR^{ad} in which R^{ad} is hydrogen or R^{ad} together with R^{ac} and the existing carbon to carbon bond forms a double bond; R^{aa} is Ar or Het; R^{ab} is hydrogen and R^{ac} is hydrogen or hydroxy or R^{ac} together with R^{ad} and

- 48 -

the existing carbon to carbon bond forms a double bond, or R^{ac} and R^{ad} together form a diradical -(CH₂)_j- in which j is an integer from 1 to 5; or R^{ab} and R^{ac} together form a diradical -(CH₂)_k- in which k is an integer from 2 to 6, or R^{ab} and R^{ac} together are oxo or dialkylaminoalkyloxyimino of formula =N-O-(CH₂)_q-NR^{ae}R^{af} in which q is the integer 2 or 3 and R^{ae} and R^{af} are independently hydrogen or (1-4C)alkyl, or the radical NR^{ae}R^{af} is 5 pyrrolidino, piperidino or morpholino;

for a radical of formula Ib, Z^b is a substituted imino group R^{ba}N or R^{ba}CH₂N in which R^{ba} is (3-7C)cycloakyl, Ar or Het; or Z^b is a disubstituted methylene group R^{bb}(CH₂)_p-C-R^{bc} in which R^{bb} is Ar or Het; p is the integer 0 or 1; and R^{bc} is hydrogen, 10 hydroxy, (1-4C)alkoxy, (1-4C)alkanoyloxy, COOR^{bd} (wherein R^{bd} is hydrogen or (1-3C)alkyl), cyano, NR^{be}R^{bf} or SR^{bg} in which R^{be} and R^{bf} are independently hydrogen, (1-4C)alkyl, (1-4C)hydroxyalkyl or (1-4C)alkanoyl, or the radical NR^{be}R^{bf} is pyrrolidino, piperidino or morpholino; and R^{bg} is hydrogen or (1-4C)alkyl; or R^{bc} forms a double bond with the carbon atom to which it is bonded and with the adjacent carbon atom in the piperidine ring;

15 for a radical of formula Ic, R^{ca} is Ar or Het; and Z^c is oxo, thio, sulfinyl, sulfonyl or imino of formula -NR^{cb}- in which R^{cb} is (1-3C)alkyl or R^{cc}R^{cd}N-(CH₂)_q- in which q is the integer 2 or 3 and in which R^{cc} and R^{cd} are independently hydrogen or (1-3C)alkyl or the radical R^{cc}R^{cd}N is pyrrolidino, piperidino or morpholino;

for a radical of formula Id, R^{da} is 1, 2 or 3;

20 for a radical of formula Ie, J^e is oxygen, sulfur or NR^{ea} in which R^{ea} is hydrogen or (1-3C)alkyl; R^{eb} is hydrogen, (1-6C)alkyl which may bear a hydroxy substituent and/or one to three fluoro substituents, (3-6C)alkenyl (in which a vinyl carbon is not bound to nitrogen), 2-hydroxyethyl, (3-7C)cycloalkyl, Ar or Het; R^{ec} is hydrogen, (1-6C)alkyl which may bear a hydroxy substituent and/or one to three fluoro substituents, (3-6C)cycloalkyl, (1-5C)alkoxy (only when J^e is oxygen), (3-6C)cycloalkoxy (only when J^e is oxygen), or an amino group of formula NR^{ed}R^{ee} containing zero to seven carbon atoms in which each of R^{ed} and R^{ee} is independently hydrogen, (1-5C)alkyl or (3-6C)cycloalkyl, or the radical NR^{ed}R^{ee} is pyrrolidino, piperidino,

morpholino, thiomorpholino (or its S-oxide) or piperazinyl (which piperazinyl group may bear a (1-3C)alkyl substituent at the 4-position);

for a radical of formula If, J^f is oxygen, sulfur or NR^{fa} in which R^{fa} is hydrogen or (1-3C)alkyl; L^f is a divalent hydrocarbon group in which the 1-position is bound to the carbon bearing the group J^f, the divalent group L^f being selected from trimethylene, cis-propenylene, 5 tetramethylene, cis-butenylene, cis-but-3-enylene, cis,cis-butadienylene, pentamethylene and cis-pentenylene which divalent group L^f itself may bear one or two methyl substituents;

for a radical of formula Ig, Z^g is (1-8C)alkyl or (3-8C)cycloalkyl which may bear one or more substituents selected from the group consisting of halo, (3-6C)cycloalkyl, cyano, 10 nitro, hydroxy, (1-4C)alkoxy, (1-5C)alkanoyloxy, aroyl, heteroaroyl, oxo, imino (which may bear a (1-6C)alkyl, (3-6C)cycloalkyl, (1-5C)alkanoyl or aroyl substituent), hydroxyimino (which hydroxyimino may bear a (1-4C)alkyl or a phenyl substituent on the oxygen), an amino group of formula NR^{ga}R^{gb}, an amino group of formula NR^{gc}R^{gd}, an amidino group of formula C(=NR^{ge})NR^{ge}R^{gf}, and a carbamoyl group of formula CON(OR^{gh})R^{gi}, but excluding any 15 radical wherein a hydroxy and an oxo substituent together form a carboxy group, wherein an amino group of formula NR^{ga}R^{gb} contains zero to seven carbon atoms and each of R^{ga} and R^{gb} is independently hydrogen, (1-5C)alkyl or (3-6C)cycloalkyl, or the radical NR^{ga}R^{gb} is pyrrolidino, piperidino, morpholino, thiomorpholino (or its S-oxide) or piperazinyl (which piperazinyl may bear a (1-3C)alkyl substituent group at the 4-position); and wherein R^{gc} is 20 hydrogen or (1-3C)alkyl and R^{gd} is (1-5C)alkanoyl, aroyl or heteroaroyl; or R^{gd} is a group of formula C(=J^g)NR^{ge}R^{gf} in which J^g is oxygen, sulfur, NR^{gg} or CHR^{gi}; and wherein the amino group NR^{ge}R^{gf} contains zero to seven carbon atoms and each of R^{ge} and R^{gf} is independently hydrogen, (1-5C)alkyl or (3-6C)cycloalkyl, or the radical NR^{ge}R^{gf} is pyrrolidino, piperidino, morpholino, thiomorpholino (or its S-oxide) or piperazinyl (which piperazinyl may bear a 25 (1-3C)alkyl substituent at the 4-position) or R^{ge} is hydrogen or (1-4C)alkyl and R^{gf} together with R^{gg} forms an ethylene or trimethylene group; R^{gg} is hydrogen, (1-4C)alkyl or together with R^{gf} forms an ethylene or trimethylene group; R^{gi} is cyano, nitro or SO₂R^{gk} and R^{gk} is (1-4C)alkyl or phenyl; R^{gh} and R^{gi} are independently (1-3C)alkyl; and in which a cyclic group which is a substituent on Z^g or formed by substitution on Z^g may bear one or more (1-3C)alkyl groups on

- 50 -

carbon as further substituents; and in which any aryl or heteroaryl group which is a part of the group Z^E may bear one or more halo, (1-4C)alkyl, (1-4C)alkoxy, cyano, trifluoromethyl or nitro substituents;

for a radical of formula I^h , G^h denotes a single bond, a double bond or a divalent hydrocarbon radical; J^h denotes a radical joined to the ring by a single bond if G^h denotes a double bond or, otherwise, a radical joined by a double bond; M^h denotes a heteroatom, a substituted heteroatom, or a single bond; and L^h denotes a hydrocarbon radical in which the 1-position is attached to M^h ; wherein the values of G^h , J^h , M^h and L^h are selected from

(a) G^h is a single bond; J^h is oxo or thioxo; M^h is oxy, thio or NR^{ha} ; and L^h is

10 L^{ha} ;

(b) G^h is a single bond; J^h is NR^{hb} ; M^h is NR^{ha} ; and L^h is L^{ha} ;

(c) G^h is a double bond, J^h is OR^{ha} , SR^{ha} or $NR^{hc}R^{hd}$; M^h is nitrogen; and L^h is L^{ha} ;

(d) G^h is methylene which may bear one or two methyl substituents; J^h is oxo,

15 thioxo or NR^{he} ; M^h is oxy, thio, sulfinyl, sulfonyl or NR^{ha} ; and L^h is L^{hb} ;

(e) G^h is a single bond; J^h is oxo, thioxo or NR^{he} ; M^h is nitrogen; and L^h is L^{hc} ;

(f) G^h is methine, which may bear a (1-3C)alkyl substituent; J^h is oxo, thioxo or NR^{he} ; M^h is nitrogen; and L^h is L^{hd} ; (g) G^h is cis-vinylene, which may bear one or two methyl substituents; J^h is oxo, thioxo, or NR^{he} ; M^h is nitrogen; and L^h is L^{he} ; and

20 (h) G^h is a single bond; J^h is oxo or thioxo; M^h is a single bond; and L^h is L^{hf} .

wherein

R^{ha} is hydrogen or (1-3C)alkyl; R^{hb} is hydrogen, (1-3C)alkyl, cyano,

(1-3C)alkylsulfonyl or nitro; R^{hc} and R^{hd} are independently hydrogen or (1-3C)alkyl or the radical $NR^{hc}R^{hd}$ is pyrrolidino, piperidino, morpholino, thiomorpholino (or its S-oxide) or

25 piperazinyl (which piperazinyl may bear a (1-3C)alkyl substituent at the 4-position); R^{he} is hydrogen or (1-3C)alkyl; L^{ha} is ethylene, cis-vinylene, trimethylene or tetramethylene which radical L^{ha} itself may bear one or two methyl substituents; L^{hb} is ethylene or trimethylene which radical L^{hb} itself may bear one or two methyl substituents; L^{hc} is prop-2-en-1-yliden-3-yl, which

-51-

radical L^{hc} itself may bear one or two methyl substituents; L^{hd} is cis-vinylene, which radical L^{hd} itself may bear one or two methyl substituents; L^{he} is methine, which radical L^{he} itself may bear a (1-3C)alkyl substituent; and L^{hf} is 4-oxabutan-1,4-diyl;

for a radical of formula Ij, X^j is (1-6C)alkyl, -CH₂OR^{ja}, -CH₂SR^{ja}, -CH₂S(O)R^{je},

5 -CH₂S(O)₂R^{je}, -COR^{ja}, -COOR^{ja}, -C(=J^{ja})NR^{jb}R^{jc}, -C(R^{ja})(OR^{jd})(OR^{je}),

-CH₂N(R^{ja})C(=J^{ja})R^{jf}, -CH₂N(R^{ja})COOR^{je} or -CH₂N(R^{ja})C(=J^{ja})NR^{jb}R^{jc};

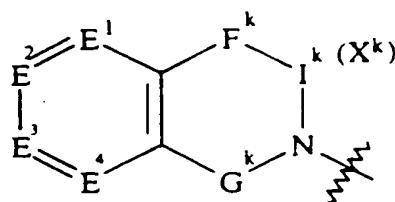
B^j is a direct bond and L^j is a hydrocarbon chain in which the 1-position is bound to B^j and L^j is selected from trimethylene, tetramethylene, cis-1-butenylene and cis,cis-butadienylene; or B^j is N(R^{jh}) and L^j is a hydrocarbon chain selected from ethylene, trimethylene and cis-vinylene; or B^j

10 is N and L^j is a hydrocarbon chain in which the 1-position is bound to B^j and L^j is cis,cis-prop-2-en-1-ylidin-3-yl; J^j and J^{ja} are independently oxygen or sulfur; R^{ja}, R^{jf} and R^{jh} are independently hydrogen or (1-6C)alkyl; R^{jb} and R^{jc} are independently hydrogen or (1-6C)alkyl; or the radical NR^{jb}R^{jc} is pyrrolidino, piperidino, morpholino, thiomorpholino (or its S-oxide) or piperazinyl (which piperazinyl may bear a (1-3C)alkyl substituent at the 4-position); R^{jd} and R^{je} are independently (1-3C)alkyl or together form a divalent hydrocarbon chain selected from ethylene and trimethylene; R^{je} is (1-6C)alkyl;

15

for a radical of formula Ik, Z^k is a nitrogen linked radical of formula II

20



II

wherein E¹, E², E³ and E⁴ form a divalent four membered chain (-E¹=E²-E³=E⁴-) in which each of E¹, E², E³ and E⁴ is methine; or in which one or two of E¹, E², E³ and E⁴ is nitrogen and the remaining E¹, E², E³ and E⁴ are methine; and further wherein one or more of E¹, E², E³ and E⁴ which is methine may bear a halo, (1-3C)alkyl, hydroxy, (1-3C)alkoxy, (1-3C)alkylthio.

(1-3C)alkylsulfinyl or (1-3C)alkylsulfonyl substituent; and wherein the radicals F^k, G^k, and I^k(X^k) are selected from

(a) G^k is a direct bond, I^k(X^k) is a radical having the formula =C(Z^k)- and F^k is a radical selected from -CH= and -N=;

5 (b) G^k is a direct bond, I^k(X^k) is a radical having the formula -C(=J^k)- and F^k is a radical selected from -N(R^{kf})-, -CH₂-CH₂- , -CH=CH-, -CH₂-N(R^{kf})- and -CH=N-;

(c) G^k is a radical having the formula -CH₂- , I^k(X^k) is a radical having formula -C(=J^k)- and F^k is selected from -CH₂- and -N(R^{kf})-; and

(d) G^k is selected from -CH₂- , -CH₂-CH₂- , -CH=CH- and -N=CH-, I^k(X^k) is a radical having the formula -C(=J^k)- and F^k is a direct bond; wherein

J^k is oxygen or sulfur; Z^k is -OR^{ka}, -SR^{ka}, -COR^{ka}, -COOR^{ka}, -C(=J^{ka})NR^{kb}R^{kc} or -C(R^{ka})(OR^{kd})(OR^{ke}); J^{ka} is oxygen or sulfur; R^{ka} and R^{kf} are independently hydrogen or (1-6C)alkyl; R^{kb} and R^{kc} are independently hydrogen or (1-6C)alkyl; or the radical NR^{kb}R^{kc} is pyrrolidino, piperidino, morpholino, thiomorpholino (or its S-oxide) or piperazinyl (which

15 piperazinyl may bear a (1-3C)alkyl substituent at the 4-position); R^{kd} and R^{ke} are independently (1-3C)alkyl or R^{kd} and R^{ke} together form ethylene or trimethylene; or Z^k is an imido radical selected from phthalimido, succinimido, maleimido, glutarimido, and 3-oxa-, 3-thia- and 3-azaglutarimido, in which the imido radical may bear one or more (1-3C)alkyl substituents and, in addition, the aromatic portion of the phthalimido may bear one or more halo, hydroxy or

20 (1-3C)alkoxy substituents; and

for a radical of formula Im, R^{ma} and R^{mb} are independently selected from the group consisting of hydrogen, (1-3C)alkyl, (3-6C)cycloalkyl, phenyl, benzyl, and phenethyl; and R^{mc} is pyrrolidino, piperidino, morpholino, thiomorpholino (or its S-oxide), piperazinyl (which piperazinyl may bear a (1-3C)alkyl substituent at the 4-position); or R^{mc} is -NR^{md}R^{me},

25 wherein R^{md} and R^{me} are independently selected from hydrogen, (1-3C)alkyl, phenyl, benzyl and phenethyl; and wherein

for a radical Q¹, Ar is a phenyl radical or an ortho-fused bicyclic carbocyclic radical of nine or ten ring atoms in which at least one ring is aromatic, which radical Ar may be

unsubstituted or may bear one or more substituents selected from halo, cyano, trifluoromethyl, (1-4C)alkyl, (1-4C)alkoxy, methylenedioxy, hydroxy, mercapto, -S(O)_nR^{x_a}, (1-5C)alkanoyl, (1-5C)alkanoyloxy, nitro, NR^{x_b}R^{x_c}, NR^{x_d}R^{x_e}, C(=NR^{x_f})NR^{x_g}R^{x_h}, CONR^{x_b}R^{x_c} and COOR^{x_j} wherein n is the integer 0, 1, or 2; R^{x_a} is (1-6C)alkyl, (3-6C)cycloalkyl or phenyl (which phenyl may bear a halo, trifluoromethyl, (1-3C)alkyl or (1-3C)alkoxy substituent); the radical NR^{x_b}R^{x_c} contains zero to seven carbons and each of R^{x_b} and R^{x_c} is independently hydrogen, (1-5C)alkyl or (3-6C)cycloalkyl, or the radical NR^{x_b}R^{x_c} is pyrrolidino, piperidino, morpholino, thiomorpholine (or its S-oxide) or piperazinyl (which piperazinyl may bear a (1-3C)alkyl substituent at the 4-position); and wherein R^{x_d} is hydrogen or (1-4C)alkyl and R^{x_e} is (1-5C)alkanoyl, benzoyl; or a group of formula C(=J^x)NR^{x_g}R^{x_h} in which J^x is oxygen, sulfur, NR^{x_f} or CHR^{x_i}; R^{x_f} is hydrogen, (1-5C)alkyl or together with R^{x_g} forms an ethylene or trimethylene diradical, the radical NR^{x_g}R^{x_h} contains zero to 7 carbons and each of R^{x_g} and R^{x_h} is independently hydrogen, (1-5C)alkyl or (3-6C)cycloalkyl, or the radical NR^{x_g}R^{x_h} is pyrrolidino, piperidino, morpholino, thiomorpholino (or its S-oxide) or piperazinyl (which piperazinyl may bear a (1-3C)alkyl substituent at the 4-position); or R^{x_g} together with R^{x_f} forms an ethylene or trimethylene diradical and R^{x_h} is hydrogen or (1-5C)alkyl; R^{x_i} is cyano, nitro, (1-5C)alkylsulfonyl or phenylsulfonyl; and R^{x_j} is hydrogen, (1-5C)alkyl or benzyl; and Het is a radical (or stable N-oxide thereof) attached via a ring carbon of a monocyclic aromatic ring containing five or six ring atoms consisting of carbon and one to four heteroatoms selected from oxygen, sulfur and nitrogen, or an ortho-fused bicyclic heterocycle derived therefrom by fusing a propenylene, trimethylene, tetramethylene or benz-diradical, which radical Het may be unsubstituted or may be substituted on carbon by one or more of the substituents defined above for Ar and may be substituted on nitrogen by (1-3C)alkyl;

Q² is a group B or CH₂B wherein B is phenyl which may bear one or two substituents independently selected from halo, trifluoromethyl, hydroxy, (1-3C)alkoxy, (1-3C)alkyl and methylenedioxy; or B is thienyl, imidazolyl, benzo[b]thiophenyl or naphthyl any of which may bear a halo substituent; or B is biphenylyl; or B is carbon-linked indolyl which may bear a benzyl substituent at the 1-position;

Q³ is hydrogen, or (1-4C)alkyl; and

-54-

Q^4 is a radical selected from $-\text{OC}(=\text{O})\text{NR}^3\text{R}^4$, $-\text{N}(\text{R}^6)\text{C}(=\text{O})\text{OR}^2$,
 $-\text{N}(\text{R}^6)\text{C}(=\text{O})\text{NR}^3\text{R}^4$, $-\text{N}(\text{R}^6)\text{C}(=\text{O})\text{SR}^5$, $-\text{SC}(=\text{O})\text{NR}^3\text{R}^4$, $-\text{N}(\text{R}^6)\text{C}(=\text{O})\text{R}^{15}$, and $-\text{OC}(=\text{O})\text{R}^{16}$
wherein:

R^2 and R^5 are independently (1-6C)alkyl, (3-7C)cycloalkyl, aryl, heteroaryl,
5 aryl(1-3C)alkyl, heteroaryl(1-3C)alkyl or a radical of formula XV, wherein any aryl or heteroaryl
group or radical of formula XV may bear one, two or three substituents independently selected
from halo, trifluoromethyl, hydroxy, (1-3C)alkoxy, (1-3C)alkyl, cyano, $-\text{NR}^7\text{R}^8$, $\text{C}(=\text{O})\text{NR}^9\text{R}^{10}$,
 $-\text{S}(=\text{O})\text{NR}^{11}\text{R}^{12}$, $-\text{S}(=\text{O})_2\text{NR}^{11}\text{R}^{12}$, and methylenedioxy, and further wherein any aryethyl,
arylpropyl, heteroarylethyl or heteroarylpropyl group may optionally be substituted at the
10 position a to the aryl or heteroaryl group by a group selected from oxo, and $=\text{NOR}^{13}$;

R^3 and R^4 are independently selected from hydrogen, (1-6C)alkyl,
(3-7C)cycloalkyl, aryl, heteroaryl, aryl(1-3C)alkyl, heteroaryl(1-3C)alkyl, and a radical of
formula XV, wherein any aryl or heteroaryl group, or radical of formula XV may bear one two or
three substituents independently selected from halo, trifluoromethyl, hydroxy, (1-3C)alkoxy,
15 (1-3C)alkyl, cyano, $-\text{NR}^7\text{R}^8$, $\text{C}(=\text{O})\text{NR}^9\text{R}^{10}$, $-\text{S}(=\text{O})\text{NR}^{11}\text{R}^{12}$, $-\text{S}(=\text{O})_2\text{NR}^{11}\text{R}^{12}$, and
methylenedioxy, and further wherein any aryethyl, arylpropyl, heteroarylethyl or
heteroarylpropyl group may optionally be substituted at the position a to the aryl or heteroaryl
group by a group selected from oxo, and $=\text{NOR}^{13}$; or

$-\text{NR}^3\text{R}^4$ taken together represents a cyclic amino radical selected from
20 pyrrolidinyl, piperidino, 1,2,3,6-tetrahydro-pyridyl, 1,2,3,4-tetrahydroquinolyl,
1,2,3,4-tetrahydroisoquinolyl, which cyclic amino radical may bear one or two substituents
independently selected from halo, trifluoromethyl, hydroxy, (1-3C)alkoxy, (1-3C)alkyl, cyano,
 $-\text{NR}^7\text{R}^8$, $-\text{C}(=\text{O})\text{NR}^9\text{R}^{10}$, $-\text{S}(=\text{O})\text{NR}^{11}\text{R}^{12}$, $-\text{S}(=\text{O})_2\text{NR}^{11}\text{R}^{12}$, phenyl, acetamidomethyl, and
methylenedioxy;

R^{15} and R^{16} are independently (1-6C)alkyl, (3-7C)cycloalkyl, aryl, heteroaryl,
aryl(1-3C)alkyl, heteroaryl(1-3C)alkyl, or a radical of formula XV, wherein any aryl or
heteroaryl group or radical of formula XV may bear one, two or three substituents independently
selected from halo, trifluoromethyl, hydroxy, (1-3C)alkoxy, (1-3C)alkyl, cyano, $-\text{NR}^7\text{R}^8$,
 $\text{C}(=\text{O})\text{NR}^9\text{R}^{10}$, $-\text{S}(=\text{O})\text{NR}^{11}\text{R}^{12}$, $-\text{S}(=\text{O})_2\text{NR}^{11}\text{R}^{12}$, and methylenedioxy,

- 55 -

E is selected from -O-, -S-, -N(R¹⁴)-, -S(=O)- and -S(O)₂-;

m is 1, 2, or 3; and

R⁶-R¹⁴ are independently selected from hydrogen and (1-3C)alkyl;

or the N-oxide of a piperidino nitrogen in Q¹;

5 or a pharmaceutically acceptable salt thereof;

or a quaternary ammonium salt thereof in which the piperidino nitrogen in Q¹ is a quadricovalent ammonium nitrogen wherein the fourth radical on the nitrogen R¹ is (1-4C)alkyl or benzyl and the associated counterion A is a pharmaceutically acceptable anion; provided that the compound of formula I is not N-phenyl-1-(2,4-dichlorophenyl)-3-piperidinopropyl

10 carbamate, N-phenyl-1-(4-methylphenyl)-3-piperidinopropyl carbamate, N-(1-isopropyl-1-naphthyl-3-piperidinopropyl)ethyl carbamate, N-phenyl-1-phenyl-3-piperidinopropyl carbamate, N-phenyl-1-phenyl-3-pyrrolidinopropyl carbamate, N-ethyl-1-phenyl-3-piperidinopropyl carbamate, or N-phenyl-1-(4-propoxyphenyl)-3-piperidinopropyl carbamate.

15 2. A compound of formula I as claimed in claim 1 wherein: Q¹ is selected from radicals of formulae Ia, Ib, Ic, Id, Ie, If, Ig, Ih, Ij and Ik; and Q⁴ is a radical selected from -OC(=O)NR³R⁴, -N(R⁶)C(=O)OR², -N(R⁶)C(=O)NR³R⁴, -N(R⁶)C(=O)SR⁵, and -SC(=O)NR³R⁴;

20 R² and R⁵ are independently (1-6C)alkyl, (3-7C)cycloalkyl, aryl, heteroaryl, aryl(1-3C)alkyl, or heteroaryl(1-3C)alkyl, wherein any aryl or heteroaryl group may bear one, two or three substituents independently selected from halo, trifluoromethyl, hydroxy, (1-3C)alkoxy, (1-3C)alkyl, cyano, -NR⁷R⁸, C(=O)NR⁹R¹⁰, -S(=O)NR¹¹R¹², -S(=O)₂NR¹¹R¹², and methylenedioxy, and further wherein any arylethyl, arylpropyl, heteroarylethyl or heteroarylpropyl group may optionally be substituted at the position a to the aryl or heteroaryl group by a group selected from oxo, and =NOR¹³; and

25 m is 1 or 2;

or the N-oxide of a piperidino nitrogen in Q¹;

or a pharmaceutically acceptable salt thereof:

or a quaternary ammonium salt thereof in which the piperidino nitrogen in Q¹ is a quadricovalent ammonium nitrogen wherein the fourth radical on the nitrogen R¹ is (1-4C)alkyl or benzyl and the associated counterion A is a pharmaceutically acceptable anion.

5 3. A compound of formula I as claimed in claim 1 wherein:

Q¹ is 4-acetamido-4-phenylpiperidino, 4-(2-methylsulfinylphenyl)piperidino, 4-(2-oxopiperidino)piperidino, or 4-(2-oxoperhydropyrimidin-1-yl)piperidino;

Q² is a group B or -CH₂B wherein B is phenyl which may bear one or two substituents independently selected from halo, trifluoromethyl, hydroxy, (1-3C)alkoxy,

10 (1-3C)alkyl and methylenedioxy; or B is thienyl, imidazolyl, benzo[b]thiophenyl or naphthyl any of which may bear a halo substituent; or B is biphenyl; or B is carbon-linked indolyl which may bear a benzyl substituent at the 1-position;

Q³ is hydrogen; and

Q⁴ is a radical selected from -OC(=O)NR³R⁴, -N(R⁶)C(=O)OR²,

15 -N(R⁶)C(=O)NR³R⁴, -N(R⁶)C(=O)SR⁵, and -SC(=O)NR³R⁴; wherein

R² and R⁵ are independently (1-6C)alkyl, (3-7C)cycloalkyl, aryl, heteroaryl, aryl(1-3C)alkyl or heteroaryl(1-3C)alkyl, wherein any aryl or heteroaryl group may bear one, two or three substituents independently selected from halo, trifluoromethyl, hydroxy, (1-3C)alkoxy, (1-3C)alkyl, cyano, -NR⁷R⁸, C(=O)NR⁹R¹⁰, -S(=O)NR¹¹R¹², -S(=O)₂NR¹¹R¹², and methylenedioxy;

20 R³ and R⁴ are independently selected from hydrogen, (1-6C)alkyl, (3-7C)cycloalkyl, aryl, heteroaryl, aryl(1-3C)alkyl, heteroaryl(1-3C)alkyl, and a radical of formula XV, wherein any aryl or heteroaryl group, or radical of formula XV may bear one two or three substituents independently selected from halo, trifluoromethyl, hydroxy, (1-3C)alkoxy,

25 (1-3C)alkyl, cyano, -NR⁷R⁸, C(=O)NR⁹R¹⁰, -S(=O)NR¹¹R¹², -S(=O)₂NR¹¹R¹², and methylenedioxy; or

-NR³R⁴ taken together represents a cyclic amino radical selected from pyrrolidinyl, piperidino, 1,2,3,6-tetrahydro-pyridyl, 1,2,3,4-tetrahydroquinolyl, 1,2,3,4-tetrahydroisoquinolyl, which cyclic amino radical may bear one or two substituents

-57-

independently selected from halo, trifluoromethyl, hydroxy, (1-3C)alkoxy, (1-3C)alkyl, cyano, -NR⁷R⁸, -C(=O)NR⁹R¹⁰, -S(=O)NR¹¹R¹², -S(=O)₂NR¹¹R¹², phenyl, acetamidomethyl, and methylenedioxy;

E is -O-;

5 m is 1 or 2; and

R⁶-R¹² and R¹⁴ are independently selected from hydrogen and (1-3C)alkyl; or the N-oxide of a piperidino nitrogen in Q¹; or a pharmaceutically acceptable salt thereof;

10 or a quaternary ammonium salt thereof in which the piperidino nitrogen in Q¹ is a quadricovalent ammonium nitrogen wherein the fourth radical on the nitrogen R¹ is (1-4C)alkyl or benzyl and the associated counterion A is a pharmaceutically acceptable anion.

4. A compound of formula I as claimed in claim 1 wherein:

Ar is phenyl which may be unsubstituted or may bear a chloro, methyl, methoxy, hydroxy or 15 methylsulfinyl substituent; Het is furyl, thienyl, 2-imidazolyl, 1,3,4-oxadiazol-2-yl, pyridyl or pyrimidinyl which ring may be unsubstituted or may bear a chloro, methyl, methoxy, hydroxy, methylsulfinyl, methoxycarbonyl or ethoxycarbonyl substituent; aryl is phenyl; heteroaryl is furyl, pyridyl, imidazolyl, indolyl or pyrimidinyl; halo is chloro or bromo; (1-3C)alkyl is methyl, ethyl, propyl or isopropyl; (1-4C)alkyl is methyl, ethyl, propyl, isopropyl, butyl, isobutyl or 20 t-butyl; (1-5C)alkyl is methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl or isopentyl; (1-6C)alkyl is methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, hexyl or isohexyl; (1-8C)alkyl is methyl, ethyl, propyl, isopropyl, isopentyl, 1-ethylpropyl, hexyl, isohexyl, 1-propylbutyl, or octyl; (3-6C)cycloalkyl is cyclopropyl, cyclopentyl or cyclohexyl; (3-7C)cycloalkyl is cyclopropyl, cyclopentyl, cyclohexyl or cycloheptyl; (3-8C)cycloalkyl is cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl; 25 (3-6C)alkenyl is allyl, 2-butenyl or 3-methyl-2-butenyl; (1-4C)alkanoyl is formyl, acetyl, propionyl, butyryl or isobutyryl; and (1-5C)alkanoyl is formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl or pivaloyl;

or the N-oxide of a piperidino nitrogen in Q¹;

30 or a pharmaceutically acceptable salt thereof;

-58-

or a quaternary ammonium salt thereof in which the piperidino nitrogen in Q¹ is a quadricovalent ammonium nitrogen wherein the fourth radical on the nitrogen R¹ is (1-4C)alkyl or benzyl and the associated counterion A is a pharmaceutically acceptable anion.

5 5. A compound of formula I as claimed in claim 1 wherein:

Ar is phenyl which may be unsubstituted or may bear a methoxy, hydroxy or methylsulfinyl substituent; Het is pyridyl or pyrimidinyl which ring may be unsubstituted or may bear a methoxy, hydroxy or methylsulfinyl substituent; heteroaryl is pyridyl; halo is chloro; (1-3C)alkyl is methyl; (1-4C)alkyl is methyl or ethyl; (1-5C)alkyl is methyl, ethyl, propyl or isopropyl;

10 (1-6C)alkyl is methyl, ethyl, propyl, isopropyl, butyl, isobutyl or t-butyl; (1-8C)alkyl is methyl, ethyl, propyl, isopropyl, 1-ethylpropyl or 1-propylbutyl; (3-6C)cycloalkyl is cyclopropyl or cyclopentyl; (3-7C)cycloalkyl is cyclopropyl or cyclopentyl; (3-8C)cycloalkyl is cyclopropyl, cyclopentyl, cyclohexyl or cycloheptyl; (3-6C)alkenyl is allyl; (1-4C)alkanoyl is formyl or acetyl; and (1-5C)alkanoyl is formyl, acetyl, propionyl, butyryl or isobutyryl;

15 or the N-oxide of a piperidino nitrogen in Q¹;

or a pharmaceutically acceptable salt thereof;

or a quaternary ammonium salt thereof in which the piperidino nitrogen in Q¹ is a quadricovalent ammonium nitrogen wherein the fourth radical on the nitrogen R¹ is (1-4C)alkyl or benzyl and the associated counterion A is a pharmaceutically acceptable anion.

20

6. A compound of formula I as claimed in claim 1 wherein:

Q¹ is 4-hydroxy-4-phenylpiperidino, 4-acetamido-4-phenylpiperidino, 4-(2-methylsulfinyl-phenyl)piperidino, 4-(2-oxopiperidino)-piperidino, or 4-(2-oxoperhydropyrimidin-1-yl)piperidino; Q² is 3,4-dichlorophenyl, or 3,4-methylenedioxyphenyl; Q³ is hydrogen; and Q⁴ is N-benzylcarbamoyloxy, N-[(S)- α -methylbenzyl]carbamoyloxy, 3-methyl-3-(2-methoxybenzyl)ureido, phenethylcarbonyloxy, 3-indan-1-ylureido, 2-methoxyphenethyl-carbonylamino, or 2-methoxybenzyloxycarbonylamino;

or the N-oxide of a piperidino nitrogen in Q¹;

or a pharmaceutically acceptable salt thereof;

-59-

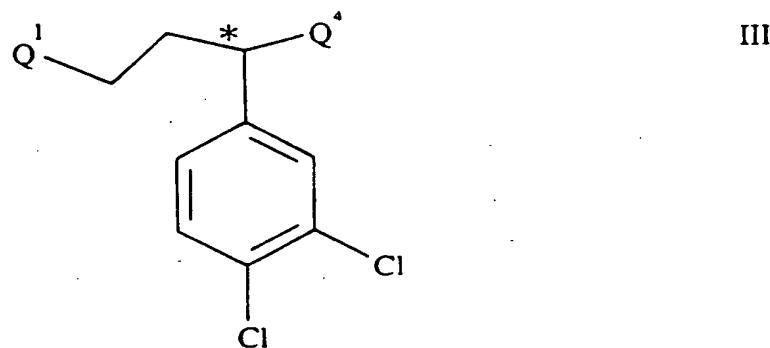
or a quaternary ammonium salt thereof in which the piperidino nitrogen in Q¹ is a quadricovalent ammonium nitrogen wherein the fourth radical on the nitrogen R¹ is (1-4C)alkyl or benzyl and the associated counterion A is a pharmaceutically acceptable anion.

5 7. A compound of formula I as claimed in claim 1 wherein:

wherein Q¹ is selected from radicals of formulae Ia, Ib, Ic, Ie, If, Ig, Ih, Ij, Ik, and Im.

8. A compound of formula I as claimed in claim 1 which is a compound of formula III:

10



wherein:

Q¹ is selected from radicals of formulae Ie, If, Ig, Ih, Ij, Ik and Im;
or a pharmaceutically acceptable salt thereof.

15

9. A pharmaceutical composition which comprises a compound of formula I;

or the N-oxide of a piperidino nitrogen in Q¹;

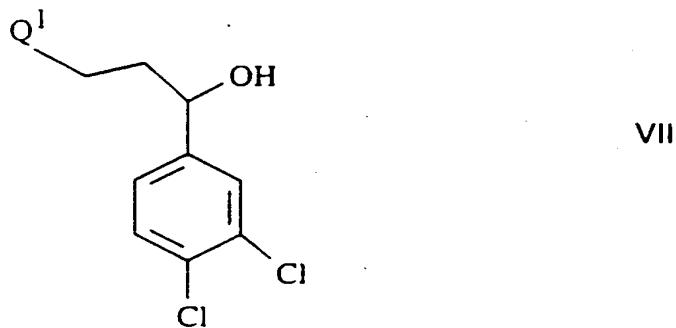
or a pharmaceutically acceptable salt thereof;

or a quaternary ammonium salt thereof in which the piperidino nitrogen in Q¹ is a quadricovalent ammonium nitrogen wherein the fourth radical on the nitrogen R¹ is (1-4C)alkyl or benzyl and the associated counterion A is a pharmaceutically acceptable; as defined in claim 1; and a pharmaceutically acceptable diluent or carrier.

- 60 -

10. A process for the manufacture of a compound of formula I ; or the N-oxide of a piperidino nitrogen in Q¹; or a pharmaceutically acceptable salt thereof; or a quaternary ammonium salt thereof in which the piperidino nitrogen in Q¹ is a quadricovalent ammonium nitrogen wherein the fourth radical on the nitrogen R¹ is (1-4C)alkyl or benzyl and the associated counterion A is a pharmaceutically acceptable anion; as defined in any one of claims 1-8, which is characterized by:

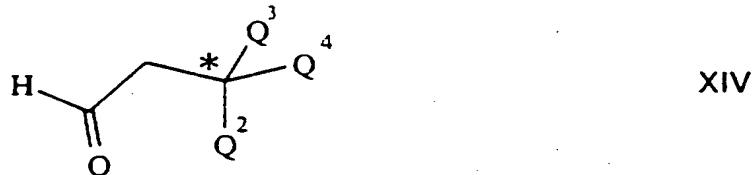
5 (a) For a compound of formula I wherein Q⁴ is an oxygen linked radical -OC(=O)NR³R⁴, reacting an alcohol of formula VII



10

with a suitable isocyanate of formula OCNR³R⁴;

(b) Alkylating an amine of formula Q¹H with an aldehyde of formula XIV;



15

by reductive alkylation;

(c) For an acid addition salt of a compound of formula I, treating a corresponding compound of formula I which is in the free-base form, with an acid

20 (d) For an N-oxide of a piperidino nitrogen in Q¹, oxidizing the piperidino nitrogen of a corresponding compound of formula I;

- 61 -

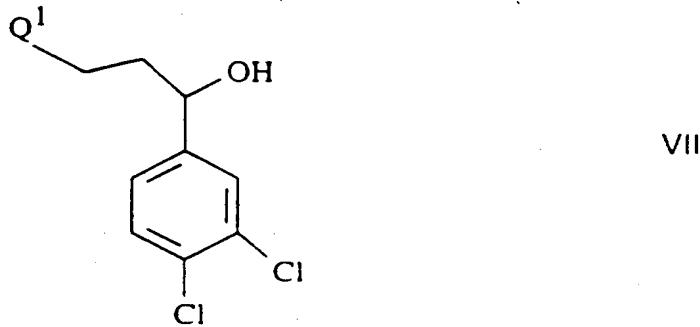
(e) For a quaternary ammonium salt of the piperidino nitrogen in Q¹, alkylating the piperidino nitrogen in a corresponding compound of formula I with an alkylating agent of formula R¹Z wherein Z is a leaving group;

5 (f) For a compound of formula I which bears a sulfinyl group, oxidizing the sulfur of a corresponding compound of formula I which bears a sulfide group;

(g) For a compound of formula I which bears a sulfonyl group, oxidizing a sulfide or sulfinyl group of a corresponding compound of formula I;

10 (h) For a compound of formula I which bears an aromatic hydroxy group, cleaving the ether of a corresponding compound of formula I which bears an aromatic alkoxy group;

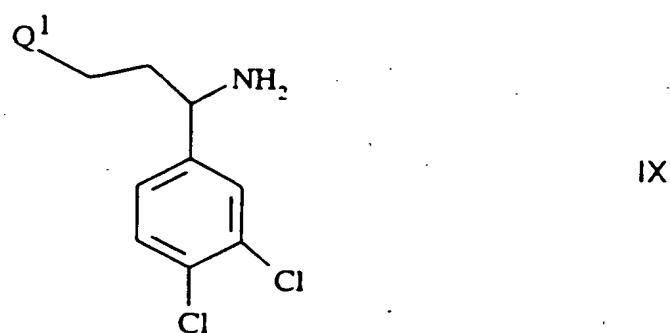
(i) For a compound of formula I wherein Q⁴ is an oxygen linked radical -OC(=O)R¹⁶, reacting an alcohol of formula VII:



15 with a suitable acid chloride of formula ClC(=O)R¹⁶ or an equivalent activated acid derivative; or

(j) For a compound of formula I wherein Q⁴ is an oxygen linked radical -NC(=O)R¹⁵, reacting an amine of formula IX:

-62-



with a suitable acid chloride of formula ClC(=O) R^{15} or an equivalent activated acid derivative.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 96/02814

A. CLASSIFICATION OF SUBJECT MATTER					
IPC 6	C07D211/58	C07D211/52	C07D211/62	C07D211/76	C07D401/04
	C07D211/66	A61K31/445			

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 680 962 A (ZENECA) 8 November 1995 see the whole document ---	1-10
X	DE 15 45 670 A (CIBA AG) 7 August 1969 see example 87 see page 4 - page 5 ---	1,4,5,7, 9
A	WO 95 21821 A (ASTRA AB, SWED.) 17 August 1995 cited in the application see the whole document ---	1-10

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- *'A' document defining the general state of the art which is not considered to be of particular relevance
- *'E' earlier document but published on or after the international filing date
- *'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *'O' document referring to an oral disclosure, use, exhibition or other means
- *'P' document published prior to the international filing date but later than the priority date claimed

- *'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- *& document member of the same patent family

2

Date of the actual completion of the international search

Date of mailing of the international search report

6 February 1997

03.03.97

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentdaan 2
NL - 2280 HV Rijswijk
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl.
Fax: (+ 31-70) 340-3016

Authorized officer

Kissler, B

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 96/02814

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FARMACO (1993), 48(4), 459-72 CODEN: FRMCE8, 1993, XP000617338 NIKOLOVA, M. ET AL: "Synthesis and pharmacological screening of a group of piperazine derivatives. Analgesic activity" Benzeneacetic acid, 1-phenyl-3-[4-(phenylmethyl)-1-piperazinyl]propyl ester see table I RN 149848-08-8 REGISTRY ---	1,4,5,7, 9
X	PROG. CLIN. BIOL. RES. (1989), 291(QSAR: QUANT. STRUCT.-ACT. RELAT. DRUG. DES.), 377-81 CODEN: PCBRD2; ISSN: 0361-7742, 1989, XP000617335 SRULEVITCH, DAVID B. ET AL: "Design, synthesis and SAR of analgesics" Propanamide, N-[1-[3-(1-oxopropoxy)-3-phenylpropyl]-4-piperidinyl]-N-phenyl- see table I RN 120448-95-5 REGISTRY ---	1,4,5,7, 9
X	PATENT ABSTRACTS OF JAPAN vol. 9, no. 78 (C-274), 6 April 1985 & JP 59 212483 A (TEIJIN KK), 1 December 1984, see abstract ---	1,4,5,7, 9
X	PATENT ABSTRACTS OF JAPAN vol. 9, no. 59 (C-270), 15 March 1985 & JP 59 193880 A (SUMITOMO KAGAKU KOGYO KK), 2 November 1984, see abstract ---	1,4,5,7, 9
X	EP 0 099 148 A (GIST-BROCADES N.V.) 25 January 1984 see claim 1 ---	1-5,7-9
X	FR 2 496 653 A (DELALANDE) 25 June 1982 Benzamide, N-[1-[(2-chlorophenyl)methyl]-3-(4-methyl-1-piperazinyl)propyl]- see page 40 RN 83659-41-0 REGISTRY ---	1,4,5,7
-/--		

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 96/02814

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>CHEMICAL ABSTRACTS, vol. 95, no. 17, 26 October 1981 Columbus, Ohio, US; abstract no. 150311. ZHU, YING-QI ET AL: "Studies on potent analgesics. I. Synthesis and analgesic activity of fentanyl derivatives" XP002024457 see abstract & YAO HSUEH HSUEH PAO (1981), 16(3), 199-210 CODEN: YHHPAL; ISSN: 0513-4870, 1981.</p> <p>---</p>	1,4,5,7, 9
X	<p>FR 1 510 206 A (CIBA LTD.) 19 January 1968 Pyrazole-1-carboxylic acid, 4-[3-[4-(o-chlorophenyl)-1-piperazinyl]-1 hydroxypropyl]-5-methyl-, ethyl ster, acetate see example 22 RN 21635-25-6 REGISTRY -----</p>	1,4,5,7, 9

2

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 96/02814

Patent document cited in search report	Publication date		Patent family member(s)	Publication date
EP-A-680962	08-11-95	JP-A-	7304767	21-11-95
DE-A-1545670	07-08-69	BE-A- CH-A- CH-A- CH-A- CH-A- CH-A- FR-M- FR-M- FR-M- FR-M- FR-M- FR-A- GB-A- NL-A- US-A-	663344 477462 477463 486473 489513 511867 4715 4716 4717 4718 4719 1463826 1096716 6505618 3478032	31-08-69 31-08-69 28-02-70 30-04-70 31-08-71 10-03-67 05-11-65 11-11-69
WO-A-9521821	17-08-95	AU-A- CA-A- EP-A- FI-A- NO-A- PL-A- ZA-A-	1826995 2181068 0743940 963128 963292 315777 9500709	29-08-95 17-08-95 27-11-96 09-08-96 07-08-96 09-12-96 11-08-95
EP-A-99148	25-01-84	NL-A- DE-A- JP-A- US-A-	8202636 3375690 59020275 4476129	16-01-84 24-03-88 01-02-84 09-10-84
FR-A-2496653	25-06-82	AU-A- BE-A- CA-A- DE-A- GB-A,B GB-A,B JP-A- LU-A- NL-A-	7875781 891526 1181748 3150876 2091250 2137992 57128660 83850 8105791	01-07-82 18-06-82 29-01-85 29-07-82 28-07-82 17-10-84 10-08-82 02-09-83 16-07-82

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 96/02814

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
FR-A-2496653		SE-A- 8107537 US-A- 4386090 US-A- 4431851 US-A- 4504663	23-06-82 31-05-83 14-02-84 12-03-85
FR-A-1510206	28-03-68	BE-A- 691637 US-A- 3470184	22-06-67 30-09-69